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R. Weil

Major Richard Weil, M. R. C.

If, in the paths of the world,
Stones might have wounded thy feet,
Toil or dejection have tried
Thy spirit, of that we saw
Nothing; to us thou wert still
Cheerful, and helpful, and firm.
—*Matthew Arnold.*

The Journal of Cancer Research records with the deepest regret the loss of its Managing Editor, Dr. Richard Weil.

Hardly had war been declared before Dr. Weil, with characteristic generosity, offered himself to the Government. He shortly received a Captain's commission in the Medical Reserve Corps and was detailed to Fort Benjamin Harrison, Indiana, where all the summer was spent in arduous preparation for new duties. Even among such a large group his ability could not but be noticed, and it was no surprise to hear, in October, that he had been advanced to the rank of Major and appointed Chief of Medical Service at the Base Hospital, Camp Wheeler, Macon, Georgia. Here he commenced his responsible task, and here, on November 19, 1917, it was completed; for, having driven himself to the point of exhaustion in attending the unusually large number of patients committed to his care, he was unable to overcome an attack of pneumonia from which one who had lived less unselfishly might have been saved.

Dr. Weil was born in New York City in 1876, and graduated from Columbia College in 1896. After having received the degree of M.D. from the College of Physicians and Surgeons, Columbia University, in 1900, he entered the German Hospital, New York, to serve as interne, and, following this, spent two years in study abroad, chiefly in Marchand's laboratory. He then returned to New York to devote himself to scientific medicine.

In 1904, he became pathologist to the German Hospital, whence he published a treatise on "Urine and Feces in Diagnosis," in collaboration with Drs. Hensel and Jelliffe. Two years later he joined the staff of the Huntington Fund for Cancer Research, and at the Loomis Laboratory initiated those investigations on the reactions of cancer and immune sera which thereafter absorbed his chief interest. His first studies concerned the hemolytic and antitryptic action of cancer serum. In 1910, he showed that the blood of syphilitics is extremely sensitive to hemolysis by cobra venom and, on the basis of this reaction, devised an exceptionally delicate clinical test for luetic infection. In a series of experiments on anaphylaxis, he elucidated this obscure condition to a notable degree by demonstrating that the sensitization is essentially cellular in origin.

In 1913, Dr. Weil became assistant director of cancer research and attending physician at the Memorial Hospital and gave much of his time to developing the organization of that institution. Here he perfected and employed the method of transfusing citrated blood. Having served also on the staffs of the Montefiore Home and Mt. Sinai Hospital, he had acquired an unusually high degree of diagnostic skill in a wide field of medicine, and, in 1915, was made professor of experimental medicine in Cornell University.

His extensive horizon is amply evident from the large number of societies to which he belonged; these included the New York Academy of Medicine, the American Medical Association, the New York State and County Medical Societies, the New York Pathological Society, the Association of American Physicians, the American Association of Pathologists and Bacteriologists, the American Association of Immunologists, and the American Society for the Control of Cancer.

His chief interest, however, was always reserved for the problems of cancer. Thus, he became one of the founders of the American Association for Cancer Research and, at the request of its Council, assumed the burden of establishing this JOURNAL, which he served most faithfully and, by reason of his thorough knowledge of the literature of cancer, most effectively. By his

untimely death American cancer research loses one of its most scholarly and accomplished workers.

The following is a list of Dr. Weil's later and more important publications:

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The hemolytic reactions of the blood in dogs affected with transplantable lymphosarcoma. Archives of Internal Medicine, 1908, i, 23.

The hemolytic reactions in cases of human cancer. Journal of Medical Research, 1908, xix, 281.

Avoidance of hemolysis in transfusion. American Journal of Surgery, 1909, xxiii, 96.

Resistance of human erythrocytes to cobra venom. Journal of Infectious Diseases, 1909, vi, 688.

An experimental study of the antitryptic activity of human serum. Archives of Internal Medicine, 1910, v, 109.

The antitryptic activity of human blood serum; its significance and its diagnostic value. American Journal of Medical Sciences, 1910, cxxxix, 714.

The biochemical investigation of malignant tumors and its diagnostic applications. Journal of the American Medical Association, 1910, lv, 1532.

Properties of ascitic fluids, especially in cases of cancer. Journal of Medical Research, 1910, xxiii, 85.

The nature of anaphylaxis, and the relations between anaphylaxis and immunity. Journal of Medical Research, 1913, xxvii, 497.

A study of the blood in rats recovered from implanted sarcoma. Journal of Experimental Medicine, 1913, xviii, 390.

Studies in anaphylaxis:

I. On the sensitizing dose in active anaphylaxis.

II. On passive sensitization by heterologous immune serum. Its duration and its prevention.

III. The phenomena of so-called saturation and displacement in anaphylaxis.

IV. "Saturation" and "displacement" in active sensitization, and in passive homologous sensitization. Journal of Medical Research, 1913, xxviii, 243.

The intravascular implantation of rat tumors. Journal of Medical Research, 1913, xxviii, 497.

The effects of colloidal copper, with an analysis of the therapeutic criteria in human cancer. Journal of the American Medical Association, 1913, lxi, 1034.

Studies in anaphylaxis:

V. Desensitization: its theoretical and practical significance. Journal of Medical Research, 1913, xxix, 233.

VI. A study of the cellular theory by the graphic method.

Studies in Anaphylaxis:
VII. The relation between antibody content and lethal dose in anaphylaxis.
VIII. The function of circulating antibody and the avidity of cellular antibody.
IX. The relation between partial desensitization and the minimal lethal dose in anaphylaxis.
X. The persistence of intracellular antigen as a factor in immunity.
XI. The share of intracellular antigen in immunity and in desensitization. Theoretical considerations. Journal of Medical Research, 1914, xxx, 87, 299.
XIII. Activation of antibody by the cell. Journal of Medical Research, 1915, xxxii, 107.

Sodium citrate in the transfusion of blood. Journal of the American Medical Association, 1915, lxiv, 425.

Chemotherapy and tumors. Journal of the American Medical Association, 1915, lxiv, 1283.

The autolysin treatment for cancer. Journal of the American Medical Association, 1915, lxv, 1641.

The treatment of parotid tumors by radium. Journal of the American Medical Association, 1915, lxv, 2138.

Studies in anaphylaxis:
XIV. On the relation between precipitin and sensitizin.
XV. Equilibrium in precipitation reactions. Equilibrium in combination.
XVI. Dissociation.
XVII. On the coexistence of antigen and antibody in the body. Journal of Immunology, 1916, i, 1.

Immunological studies in pneumonia. Journal of Experimental Medicine, 1916, xxiii, 1.

Note on skin reaction in pneumonia. Journal of Experimental Medicine, 1916, xxiii, 11.

Chemotherapeutic experiments on rat tumors. Journal of Cancer Research, 1916, i, 95.

Studies in anaphylaxis:
XVIII. The mechanism of delayed shock. Journal of Immunology, 1916, ii, 95.
XIX. Simultaneous injections of antigen and antiserum. Journal of Immunology, 1916, ii, 109.

The immune reaction to tuberculous infection. Journal of the American Medical Association, 1917, lxviii, 972.

The vasomotor depression in canine anaphylaxis. Journal of Immunology, 1917, ii, 429.

The relation between antigen and antibody in the living animal. Journal of Immunology, 1917, ii, 399.

Studies in anaphylaxis:
XX. The reciprocal relations of antigen and antibody within the cell. Journal of Immunology, 1917, ii, 469.

Studies in anaphylaxis:

XXI. Anaphylaxis in dogs. A study of the liver in shock and in peptone poisoning. Journal of Immunology, 1917, ii, 525.

XXII. Anaphylactic reactions of the isolated dog's liver. Journal of Immunology, 1917, ii, 571.

EXPERIMENTAL STUDY OF THE PATHOGENESIS OF CARCINOMA[1]

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The problem of the etiology of tumors, and in particular of carcinoma, has been investigated for a great many years, but has not yet been solved. Many suggestions have been offered, among which Virchow's and Cohnheim's are especially prominent; both of these, however, were the result of clinical experience rather than of experimental study; hence, the adherents of these hypotheses have tried subsequently to establish them by means of experiments, the object of which has been artificially to produce carcinoma. But all attempts have proved negative, until Fibiger (1), of Copenhagen, finally succeeded in producing papilloma and carcinoma in the stomach and the esophagus of rats by infecting them with spiroptera; the origin of these new growths he referred to irritation of the mucous membrane of the stomach and the esophagus by the parasite. Thus the soundness of Virchow's irritation hypothesis has been demonstrated experimentally for the first time.

To this problem we also have devoted ourselves for four years (12, 13, 14, 15, 16, 17, 18, 19, 20), pursuing experiments in accordance with Yamagiwa's view (2), which he has expressed as follows: The repetition or continuation of chronic irritation may cause a precancerous alteration in epithelium previously normal. If the irritant continue its action, carcinoma may be the outcome, even though no specific agent has been interpolated.

[1] The authors have not read the proof of this article.

For our experiments, we have employed mainly the ear of the domestic rabbit, an organ in which no spontaneous new growth has ever been reported. Among the methods of mechanical or chemical irritation chosen, the painting of coal-tar upon the inner surface of the ear has been the most efficacious in producing carcinoma.

The investigations are being continued, but we wish to report here a summary of the results up to June 30, 1916.

We have tried various methods (table 1) of irritating the epithelium and subcutis, and with each of them have produced, as Fischer (9), Haga (10), Jores (3) and others have done, an

TABLE 1

Methods, and number of experiments

	EXPERIMENT				TOTAL
	I	II	III	IV	
	Coal-tar painting of inner surface of ear every two or three days	Coal-tar painting of outer surface of ear every two or three days	Coal-tar painting of incised wounds on margin of ear every two or three days	Coal-tar painting on outer surface of ear every two or three days after repeated intradermal injection of scarlet oil	
Number of rabbit ears employed......	50	26	31	30	137

atypical growth of the epithelium (12); but of all the methods, painting with coal-tar was most effective, as has been said, and it had the additional advantage, furthermore, of being a simple procedure.

It was hoped that epithelium which had once begun a career of atypical growth would proliferate more and more atypically as the applications of coal-tar were continued, until at last it acquired a true malignant character; for the occurrence of carcinoma in coal-tar workers has become well known since the investigations of Vollkmann (4), Liebe (4), Tillmanns (5), and Schuchardt (6); and while coal-tar carcinoma has not yet been experimentally produced, it is nevertheless conceivable that one

might succeed if suitable methods of applying this irritant could be discovered.

Only Cazin (7) and Bayon (8) appear to have employed coal-tar for an experimental investigation of the pathogenesis of carcinoma. The former brushed this material upon the inner surface of a dog's ear, while the latter injected hypodermically a mixture of watery extract of coal-tar and lanolin; neither, however, produced more than a temporary atypical growth of the epithelium.

TABLE 2

A. The result with regard to the rabbits in four earlier experiments which have survived over 70 days

NUMBER OF RABBITS AND EARS IN EACH EXPERIMENT		NUMBER OF EARS BEARING FOLLICULO-EPITHELIOMA AMONG THE SURVIVING RABBITS	PERCENTAGE RESULT BETWEEN 2 AND 3
Rabbits	Ears		
			per cent
15	23	20	87
6	6	4	67
7	13	7	54
10	10	1	10
B. The result with regard to rabbits which have survived over 150 days			
9	13	13	100
3	3	3	100
4	7	7	100
6	6	1	17

The results of our own investigations with coal-tar have gradually approached our expectations; *folliculoepitheliomata*[2] have arisen in nearly all ears after a period longer than 100 days (table 2) from the beginning of the application, numbering in one instance twenty on a single ear. The size of the lesions varied from that of a grain of rice to that of a sparrow's egg. Some later showed a more malignant character and it could be proved, in fact, both macroscopically and microscopically, that we had produced from them eight cases of carcinoma in its

[2] We employ the term *folliculoepithelioma* for papillomatous new growths which reach the size of a rice grain; a full explanation of this term will be given in a succeeding paragraph.

earliest stage, sixteen cases of carcinoma in an early stage, and seven cases of still more fully developed carcinoma. Furthermore, we were able to demonstrate the presence of metastases in the lymph nodes at the root of the ear and in the submaxillary region in two cases among the last seven of carcinoma.

CLINICAL COURSE OF THE LESIONS

We have divided the course of events into four periods: a first period, characterized by atypical growth of the epithelium (before the appearance of folliculoepithelioma); a second, marked by the appearance of folliculoepithelioma benignum; a third, in which folliculoepithelioma malignum (carcinomatous alteration in a folliculoepithelioma) arises; and a fourth period, that of metastasis.

First period: Atypical growth of the epithelium. After applications of coal-tar had been begun the rabbits appeared uneasy and the irritated ear soon became swollen. One week later the epithelium, especially that of the hair follicles, appeared hyperkeratotic; cystic dilatation of the follicles set in, and keratin was retained in them. At the same time, also, the hair began to come out. These changes became gradually more distinct during the period of 30 to 360 days.

Second period: Appearance of folliculoepithelioma. About 50 days after irritation had been begun, we noticed certain circumscribed regions in which the epithelium of one or more hair follicles was hyperkeratotic to a high degree. These areas became gradually more and more elevated, and eventually developed into papillomatous new growths which were very variable in size and shape, though roughly divisible into two groups: *Pedunculated* and *sessile.* The largest of the former attained approximately the size of a nut, some, however, being larger. In some cases, the interstitial connective tissue increased in amount, the growths then appearing like fibroepitheliomata or fibromata. The sessile tumors measured over 1 cm. in diameter across the base. On the cut surface of all these growths there were visible a number of dilated hair follicles, in

which keratin had accumulated. Many of the tumors continued to grow after the irritant had been withdrawn (provided it had been applied for a sufficiently long period), more and more of the horny substance accumulated in the dilated follicles, and finally these neoplasms came to resemble the cutaneous horns found in the human subject. If broken off at the base, new horns grew again at the same site or from the neighbouring epithelium.

Third period: Production of carcinoma. In the course of continued application of coal-tar to these new growths, the cut surface of some of them became so irregular that we could not differentiate macroscopically one hair follicle from another. The microscope showed a high degree of atypical proliferation of the epithelium (carcinoma in its earliest stage). The surface of these new growths then ulcerated, the tumors increased in size, and the walls of the ulcers gradually thickened, so that they came to resemble rodent ulcer. Microscopic examination disclosed an early stage of carcinoma. Certain of these growths continued to increase in dimension until they imitated even macroscopically the carcinomata of man. Thus our first and fifth cases presented elevated nodules which had, under the microscope, the appearance of a carcinoma more advanced than those described as being in an early stage. The second, fourth, sixth, and seventh cases of carcinoma arose from sessile folliculoepitheliomata, while the third developed from a pedunculated tumor. The second, third, fourth, sixth, and seventh cases of carcinoma were, both macro-and microscopically, the most typical carcinomata in our series.

Fourth period: Metastasis. The third, fourth, sixth, and seventh cases, among these seven examples of experimentally produced carcinoma, exhibited a swelling of the regional lymph nodes, and in the fourth and the sixth cases these nodes were proved by the microscope to contain metastatic deposits from the primary tumor. The nodes of the third case were the seat of a suppurative adenitis, yet it is conceivable that they may have contained carcinomatous metastases before the infection developed; those of the seventh have not yet been extirpated, but it may be supposed that they contain metastatic deposits,

inasmuch as the primary tumor was more advanced than either of the two in which metastasis was definitely proved.

Microscopical observation demonstrated that the carcinomata originated in folliculoepitheliomata, passing step by step through various stages until they reached that of completely developed carcinoma. Since the sequence of events was similar in all, we shall briefly describe here only the representative cases of carcinoma (third, fourth, sixth, and seventh cases).

Third case of carcinoma

This growth arose on the inner surface of the right ear in a black female rabbit, about two years old, in which applications of coal-tar had been begun on December 15, 1914, and repeated every two or three days. Seventy-five days after the first painting, a pedunculated papilloma was found in the irritated area; this tumor grew slowly until, 111 days later, it had become more and more hyperkeratotic, had assumed the sessile form, and had ulcerated. It spread along the surface and its edges thickened gradually, so that it came to resemble a rodent ulcer; but it seemed to invade the deeper tissues also, an area on the outer surface of the ear opposite to it becoming gradually elevated and finally ulcerating. After 130 days, the ear was perforated by an opening that soon became large enough to admit the little finger, and finally extended to the free border (fig. 12).

On the 151st day small pieces from the thickened wall of this perforating ulcer were removed for microscopical examination. The microscope showed that the new growth had already become malignant, resembling a carcinoma in its epithelial pearls and columns of epithelium; furthermore, there could be demonstrated the formation of thrombi in the veins, and a remarkable infiltration of the surrounding tissues.

The lymph nodes at the root of the affected ear began to swell after perforation had occurred, and reached the size of a large nut before the animal died. As they were the seat of suppurative adenitis, it is impossible to say whether or not they contained metastases.

The tumor in this rabbit continued to increase in size until the animal died from emaciation on the 180th day.

Fourth case of carcinoma

This is a case in which the occurrence of metastasis was proved.

The new growth arose on the inner surface of the ear of a two year old, black, male rabbit, weighing 2560 grams at the beginning of the experiment (June 16, 1915). One hundred and thirty-three days later we observed that a small papillomatous growth (the early phase of folliculoepithelioma) the size of a grain of rice, had arisen from a whitish spot on the irritated surface. On the 165th day its diameter measured 2.3 cm. and its surface had become ulcerated. The ulcerated surface was elevated above the level of the surrounding epithelium, and the wall of the ulcer gradually thickened, so that the growth came to resemble macroscopically a rodent ulcer. Two-thirds of the tumor was removed, together with the ear cartilage and the epithelium of the opposite side (outer surface), and the growth was inoculated into the subcutaneous tissues of the back and the ear in 20 rabbits. Microscopical investigation of the extirpated sample proved that the neoplasm had already assumed the characteristics of carcinoma, the nodule exhibiting those features of "carcinoma in its early stage" which we shall describe in a following paragraph.

The remainder of the tumor, left in situ, showed an inclination to diminish in size for a while after the operation, but it gradually regained its dimensions and on the 273d day (76 days after the operation, March 15, 1916) its diameter had reached 2.8 cm. At that time we observed a nodule on the outer surface of the ear in a situation corresponding to that of this growth on the inner surface; the new nodule, like the primary tumor, finally ulcerated. The irritant was then discontinued to see whether the tumors would continue to grow in its absence. This proved to be the case, for the nodule grew slowly, spreading along the surface, and the lymph nodes at the root of the ear began to swell; furthermore, the animal commenced

to lose weight. On the 294th day both ulcers had increased still more in size, the regional lymph nodes had enlarged to about the size of a peanut, and emaciation had become even more noticeable.

On the 350th day the primary ulcer on the inner surface of the ear measured 5.2 cm. by 5.3 cm., and the secondary one on the outer surface 3.5 cm. by 4.5 cm. One of the lymph nodes at the root of the ear had attained nearly the size of a sparrow's egg, and the others the size of a peanut. On the 351st day these nodes were extirpated, and inoculated, in small fragments, into the subcutaneous tissue of the back in 10 rabbits. That portion reserved for histological examination contained no metastatic deposits, and the result of the transplantation was negative. On the 366th day (June 16, 1916) the animal died, extremely emaciated, its weight having been reduced almost to half the body weight at the time of the first coal-tar application. The tumor had continued to grow, and when the rabbit died the neoplasm was about twice as large as when the irritant was discontinued (on the 273d day); its size was now 5.5 cm. by 6.5 cm., while the secondary nodule was 4.5 cm. by 5.2 cm.

At the post mortem examination, solid and cystic metastatic nodules varying from miliary size to the dimensions of a soja peanut were discovered in the two lymph nodes at the root of the ear and in one of the submaxillary nodes; the former were found, upon microscopic examination, to consist of accumulations of cancer cells, while the latter contained a mucous fluid in which yellowish flocculi, composed of degenerated epithelial cells and leucocytes, were suspended. The walls of such cysts were covered with a many-layered epithelium which, in several places, had formed epithelial pearls and was infiltrating the lymph sinus and the surrounding tissues. One of the enlarged submaxillary nodes yielded similar findings. In no other organ, however, were we able to find either gross or microscopical evidence of metastasis.

Sixth case of carcinoma

In this case, also, the occurrence of metastasis was proved. The tumor arose on the inner surface of the right ear of a white female rabbit about two years old, and weighing 2750 grams when the experiment was begun on July 2, 1915.

On the 261st day we observed a small elevation on the irritated surface; on the 292d day this nodule, which now measured 0.7 cm. by 0.5 cm., ulcerated. On the 302d day its diameter was 1 cm., and on the 312th day two lymph nodes at the root of the ear began to enlarge, the tumor having, in the meantime, attained a diameter of 1.3 cm.

On the 322d day (May 20, 1916) the animal began to emaciate; on this date the coal-tar was discontinued. On the 332d day the two swollen lymph nodes had reached about the size of a peanut, and the ulcerated tumor continued to enlarge, even though the applications of coal-tar had been stopped. On the 337th day the new growth measured 1.0 cm. by 1.5 cm., and the enlarged nodes had attained almost the size of a nut. The lymph nodes were extirpated and small fragments inoculated subcutaneously into 10 rabbits, but the result was negative. At the operation these nodes were found adherent to the surrounding tissues, a condition which the microscope proved to be due to the infiltrative growth of carcinomatous metastases into them. The cut surface of the node exhibited a cystic nodule about the size of a pea, with contents similar to those of the one just described. The cyst was lined by many layers of cancer cells and other parts of the node contained accumulations of these elements, but epithelial pearls could not be demonstrated. The node, therefore, undoubtedly contained metastases.

On the 338th day the rabbit died, extremely emaciated (1750 grams). The ulcerated folliculoepithelioma resembled human carcinoma in its histological aspects. The rest of the post-mortem findings were negative; in particular, neither macroscopic nor microscopic evidence of metastases in remote regions could be discovered.

Seventh case of carcinoma

This tumor developed from a cutaneous horn. It arose on the inner surface of the right ear of a two year old, brown, female rabbit after long continued irritation with coal-tar (November 19, 1914, to June 12, 1916); after the 205th day the irritant was discontinued, in order that the behavior of the lesion in the absence of its exciting cause might be observed.

By the 205th day two sessile and two pedunculated folliculoepitheliomata had arisen, and on the 305th day many new sessile folliculoepitheliomata were observed; nearly all these tumors continued to enlarge and developed into cutaneous horns, one of which gave origin to a carcinoma (seventh case); it is this one in particular which we now wish to discuss.

This, the seventh case of carcinoma, arose on the 286th day from a diffusely elevated spot on the irritated surface, which elevated and enlarged gradually until it had become a sessile folliculoepithelioma, and, by the 508th day, a cutaneous horn; it grew both in length and width, measuring on the 513th day 1.5 cm. by 1 cm. It was conical in shape, the free end was hard and dry, and the base elastic and soft. On the 518th day a small area at the base ulcerated, and on the 520th day the free end of the horn fell off; the portion now remaining consisted of an ulcer with edges elevated 0.5 cm. from the surrounding epithelium and an even, finely granulated surface.

On the 543d day (May 15, 1916) the diameter of this ulcer had reached 1.5 cm., and a small diffuse elevation was noticed on the opposite (outer) surface of the ear, which became gradually larger and at last ulcerated like the primary folliculoepithelioma on the inner surface. There was considerable venous engorgement. On the 565th day the primary ulcer was 2.3 cm. by 1.5 cm., and the lymph nodes at the root of the ear began to swell, one of them being about the size of a soja peanut; both ulcer and nodes continued to increase in size. A fragment removed for microscopical examination had all the characteristics of a rodent ulcer; the epithelium had infiltrated into the lymph vessels and the veins and formed a thrombosis of car-

cinoma cells in them; furthermore, it had penetrated the ear cartilage and had reached the subcutaneous tissue on the opposite side, where it produced on the outer surface the ulcer just mentioned. This case is still under observation, the animal being still well, and the lymph nodes will be transplanted as soon as they are large enough.

The four cases of carcinoma just described exhibited the following macroscopic and microscopic signs of spontaneous carcinoma: (1) Exhaustion and emaciation, resembling the cachexia of cancer patients. The animal in which the seventh case of carcinoma arose is not yet emaciated, it is true, but this may be because the carcinoma is still fairly recent. (2) The tumors infiltrated the subcutaneous tissue, the lymph channels, and the blood-vessels, and exhibited the histological features characteristic of rodent ulcer. Again, these carcinomata grew not only in the presence of the irritant, but also after it had been discontinued; thus in the fourth case of carcinoma the tumor doubled in size in the 93 days following the withdrawal of the coal-tar applications. (3) The presence of metastases was proved in the regional lymph nodes in the fourth and sixth cases.

Such facts make it evident that these experimentally produced carcinomata closely resemble carcinoma in man, and especially that type found among workers in coal-tar.

HISTOLOGY OF THE LESIONS

As we have in the preceding paragraphs, divided the course of our experiments into four periods, according to the macroscopical findings, so we wish to discuss in the following pages the microscopical appearances characteristic of these four periods.

First period: Atypical growth of the epithelium. The epithelium, and especially that at the periphery of the hair follicles, gradually undergoes hyperplasia; (1) each layer increases considerably in thickness; (2) many symmetrical mitoses are found in its basal layer; (3) the hair follicles become cystic; (4) the basal layer grows irregular in outline, owing to the projection

of processes which ramify in the surrounding subcutaneous tissues. These are the earliest stages in the development of folliculoepithelioma benignum and malignum. Furthermore, the blood-vessels, especially the veins and capillaries, soon dilate, while eosinophiles and lymphocytes escape into the neighboring connective tissues. The duration of this period is very variable; according to the individual animal it may occupy from 30 to 350 days, the average being about 100 days.

Second period: Appearance of folliculoepithelioma. The circumscribed papillomatous elevations on the irritated surface, which we have already described, consist of one or more hair follicles; in them, hyperplasia and hyperkeratosis of the epithelium are present in high degree, the process resembling that seen in the first period already mentioned, except that it is more advanced. From these elevations arose new growths, which we divide into two general types, *pedunculated folliculoepithelioma* and *sessile folliculoepithelioma,* though they are very variable both in size and shape.

(1) Pedunculated folliculoepithelioma: This arises when hair follicles in the central or the peripheral part of the papillomatous epithelial elevation are lifted upward by the pressure of epithelial growth, and continue to proliferate. As these new growths arise primarily from the epithelium of the hair follicle, we call them folliculoepithelioma rather than papilloma. In their subsequent growth, some of these pedunculated folliculoepitheliomata underwent an increase in their connective tissue, thus becoming fibromatous; others came to resemble the sessile type; and still others (10 in all) developed into cutaneous horns.

(2) Sessile folliculoepithelioma. This type arose from one or more hair follicles when the papillomatous epithelium showed a higher degree of hyperplasia and hyperkeratosis. The cystic hair follicles are arranged almost directly on the ear cartilage, and the epithelium and corium extending upward between them form septa or papillary processes, the spaces between which are filled with collections of concentric keratinized epithelial cells. Hence these new growths have wide bases, and are

elevated but little from the surface of the skin; occasionally, however, one or more hair follicles may push upward, as in the pedunculated variety. Thirty-four of these sessile folliculoepitheliomata developed into cutaneous horns when we stopped the coal-tar.

Some of these cutaneous horns diminished gradually in size and at last disappeared, but an equal number continued to grow for 365 days after the coal-tar had been discontinued.

The blood-vessels, especially the veins and capillaries, become greatly dilated, and eosinophiles and lymphocytes are found in the interstitial connective tissue. Many symmetrical bipolar mitotic figures occur in the basal layer of the epithelium. Mucous degeneration of the interstitial tissue was not found in these folliculoepitheliomata.

Third period: Production of carcinoma. This period we have divided into three stages:—(1) earliest stage of carcinoma; (2) early stage of carcinoma; (3) fully developed carcinoma.

(1) Earliest stage of carcinoma. It is difficult to differentiate these very young carcinomata from benign folliculoepithelioma. However, the following characteristics will help in the differential diagnosis. All or a part of the epithelium of these new growths assumes a fainter stain with hematoxylin than does normal epithelium or that of the benign folliculoepithelioma; the sprout-like processes, developed by atypical proliferation of the basal epithelium of the hair follicle become more angular at their basal layer, and the processes grow very irregular in thickness; the interstitial connective tissue becomes loose or shows a slight mucous degeneration; lateral and downward penetration of the cancerous epithelium can be demonstrated.

We believe that such changes as these must be the initial step in the transformation to carcinoma.

Eight cases of carcinoma in the earliest stage were discovered among seven irritated ears (see tables 3, 4, and 5).

(2) Early stage of carcinoma. By prolonging the irritation, we have produced many cases of folliculoepitheliomata exhibiting more advanced changes than are found in the earliest stage

of carcinoma. Such tumors show the following characteristics:—the interstitial connective tissue becomes loose and edematous, the sprout-like processes in the basal layer of the hair follicles are more angular than in the first stage, these sprouts grow even more irregular in thickness, lateral and downward invasion takes place to a higher degree than in the previous stage, and the invading processes anastomose with one another to form a network; the intercellular spaces become wider (*dissociation*) and individual cells leave the main group (*emancipation*); the epithelium takes a fainter stain with hematoxylin than does normal epithelium or that exhibiting atypical growth; two among these cases showed invasion of the veins, and one into the lymphatic channels; the dilatation of the capillaries and the veins is generally more advanced than in the first period.

TABLE 3

Experimentally produced malignant folliculoepithelioma

CASES		EXPERIMENTAL SERIES	SEX	SIDE	DAYS ELAPSED BEFORE MICROSCOPICAL DIAGNOSIS COULD BE MADE	DAYS TO DEATH OF RABBIT
Carcinoma	1st case	III	♀	Right	179	222
	2d case	I	♀	Right	103	103*
	3d case	I	♀	Right	151	180
Carcinoma in its early stage	1st case	I	♀	Right	103	103*
	2d case	I	♀	Left	103	103*
	3d case	I	♀	Right	103	103*
	4th case	I	♂	Left	103	183
Carcinoma in its earliest stage	1st case	I	♀	Left	103	103*
	2d case	II	♀	Left	156	156
	3d case	II	♀	Left	194	255

* The second case of complete carcinoma, the first, second, and third cases of carcinoma in its early stage, and the first case of carcinoma in its earliest stage, were all seen in one rabbit.

These are, in general, the characteristics of our carcinomata in their early stage, but the process varies in intensity, and some of the lesions resembled complete carcinoma. The find-

TABLE 4

CASES		SEX	SIDE	DAYS NECESSARY FOR MICROSCOPIC DIAGNOSIS	DAYS TO DEATH OF RABBIT	REMARKS
Carcinoma..	4th case	♂	Right	197	366	Metastasis proved in the regional lymph nodes
	5th case	♀	Right	120	120	This rabbit bore the eleventh case of carcinoma in its early stage
	6th case	♀	Right	338	338	Metastasis proved in the regional lymph nodes; this rabbit bore three cases of carcinoma in its early stage
Carcinoma in its early stage......	5th case	♀	Left	338	338	These three cases of carcinoma in its early stage were produced in the same rabbit which bore the sixth case of carcinoma
	6th case	♀	Right	338	338	
	7th case	♀	Right	338	338	
	8th case	♂	Left	238	238	
	9th case	♀	Right	128	128	
	10th case	♂	Right	118	118	This rabbit bore the fourth case of carcinoma in its earliest stage
	11th case	♀	Left	120	120	This rabbit bore the fifth case of carcinoma
	12th case	♀	Right	90	90	These cases produced in the same rabbit
	13th case	♀	Left	90	90	
	14th case	♀	Left	90	90	
	15th case	♂	Right	55	55	
Carcinoma in its earliest stage......	4th case	♂	Left	118	118	This rabbit bore the tenth case of carcinoma in its early stage
	5th case	♂	Right	257	257	
	6th case	♀	Left	192	192	
	7th case	♀	Right	256	256	These cases produced in the same animal
	8th case	♀	Right	256	256	

ings are like those described by Ribbert and others in early carcinoma.

So far we have produced sixteen cases of carcinoma in its early stage among thirteen ears in ten rabbits (see tables 3, 4, and 5).

(3) Fully developed carcinoma. Our seven cases of carci-

noma, which arose after further repetition of the coal-tar applications, resembled closely in their histological characteristics the spontaneous carcinomata of man. The features distinguishing the previous stage become more advanced, especially the infiltrative growth of the epithelium. This is now really striking, the carcinomatous cells invading the surrounding subcutaneous tissue both downward and laterally, growing into the veins and the lymphatic channels, penetrating the aural cartilage, and forming ulcerated new growths of a similar nature on the opposite surface of the ear. Mucous degeneration of the interstitial connective tissue was noticed in almost all cases of carcinoma, especially in the second, fourth, and sixth cases. The first, second, and fifth were less developed than the other four (the third, fourth sixth, and seventh), which showed in higher degree almost all the characteristics mentioned above, and resembled spontaneous carcinoma both macroscopically and microscopically.

TABLE 5

Carcinoma developing from cutaneous horns

CASE	SEX	SIDE	DAYS NECESSARY FOR MICROSCOPIC DIAGNOSIS	DAYS TO DEATH OF RABBIT	REMARKS
7th case of carcinoma	♀	Right	565	589 (still living)	These tumors developed from cutaneous horns in the second case of cutaneous horns in the first experiment (see table 6)
16th case of carcinoma in its early stage	♀	Left	565	589 (still living)	

These seven cases of carcinoma occurred on the inner surface of seven ears in seven rabbits.

Fourth period: Metastasis. This has been already discussed under other headings.

Other problems concerning the histogenesis of experimentally produced carcinoma in the rabbit have been already suggested in previous reports, but will be taken up again in full (20).

APPENDIX

Experiments on the artificial production of cutaneous horns

Three rabbits remaining from the first experiment were used for this investigation, the purpose of which was to observe the fate of the experimentally produced new growths after painting with coal-tar had been discontinued. The experiment began on June 12, 1915. To our surprise, the great majority of the

TABLE 6

First experiment

CASES	SIDE	DAYS TREATED	DAYS AFTER TREATMENT WAS DISCONTINUED	DAYS FROM BEGINNING OF EXPERIMENT	NUMBER OF CUTANEOUS HORNS DEVELOPING FROM FOLLICULOEPITHELIOMATA			NUMBER OF FOLLICULOEPITHELIOMATA UNCHANGED OR DECREASING IN SIZE		
					From sessile folliculoepitheliomata	From pedunculated folliculoepitheliomata	Total	Sessile folliculoepitheliomata	Pedunculated folliculoepitheliomata	Total
1st.......	Left	172	384	556	8	1	9	0	0	0
	Right	172	384	556	5	0	5	0	0	0
2d.......	Left	205	384	589	1	1	2	0	1	1
	Right	205	384	589	2	0	2	0	2	2
3d.......	Left	422	135	557	3	3	6	1	0	1
	Right	422	135	557	5	5	10	1	2	3
Total..........					24	10	34	2	5	7

folliculoepitheliomata developed into cutaneous horns (see table 6). This outcome was so interesting that one of us (Ichikawa) continued this investigation into the pathogenesis of cutaneous horns (see table 7), and found that 34 among 45 sessile folliculoepitheliomata developed into horns (75%) and 10 among 19 pedunculated folliculoepitheliomata (53%). The folliculoepitheliomata which did not develop into horns gradually decreased in size and finally vanished, though a few of them first underwent a secondary fibromatous alteration.

Most of the cutaneous horns increased in size after the appli-

cations of tar had been discontinued, and, furthermore, we observed horns developing from the neighbouring epithelium. Thus there was required for the production of cutaneous horns the application of coal-tar for a certain length of time, followed by a period of freedom from irritation. In the further course of the experiment, one of these horns gradually took on the char-

TABLE 7

Second experiment

CASES	SIDE	DAYS TREATED	DAYS AFTER TREATMENT WAS DISCONTINUED	DAYS FROM BEGINNING OF EXPERIMENT	NUMBER OF CUTANEOUS HORNS DEVELOPING FROM FOLLICULOEPITHELIOMATA			NUMBER OF FOLLICULOEPITHELIOMATA REMAINING UNCHANGED OR DECREASING IN SIZE		
					From sessile folliculoepitheliomata	From pedunculated folliculoepitheliomata	Total	Sessile folliculoepitheliomata	Pedunculated folliculoepitheliomata	Total
1st	Left	239	141	380	2	0	2	0	0	0
2d	Right	239	141	380	0	0	0	1	0	1
3d	Left	191	147	338	0	0	0	0	1	1
4th	Right	191	147	338	0	0	0	1	1	2
5th	Left	239	141	380	1	0	1	0	0	0
6th	Left	223	34	257	2	0	2	0	0	0
7th	Right	239	18	257	0	0	0	3	0	3
8th	Left	239	141	380	2	0	2	0	0	0
9th	Left	208	48	256	1	0	1	0	1	1
10th	Right	208	48	256	1	0	1	0	0	0
11th	Left	184	54	238	0	0	0	2	1	3
12th	Left	264	97	361	1	0	1	2	0	2
Total					10	0	10	9	4	13

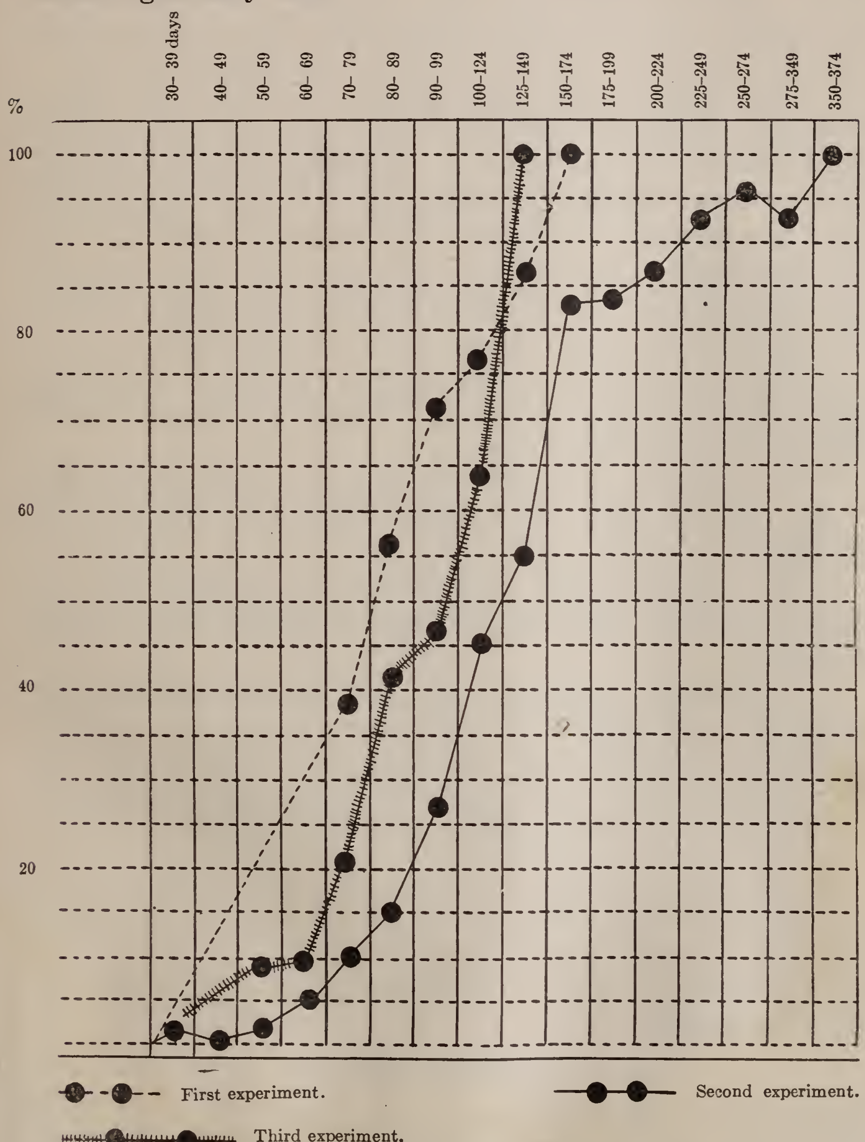
acter of an early carcinoma and another that of a carcinoma in a somewhat more advanced stage (see table 5). The details have already been discussed in the preceding paragraphs.

SUMMARY

The following conclusions may be drawn:

1. Papillomatous new growths (which we term folliculo-epitheliomata) may be produced on the rabbit's ear by the ap-

plication of coal-tar for 30 to 100 days (text figure 1). The proportion of folliculoepitheliomata to the total number of ears treated gradually rises



Text Fig. 1. Gradual rise in percentage of folliculoepitheliomata with the passage of time.

2. By the repeated application of coal-tar, eight cases of carcinoma in its earliest stage, sixteen in an early stage, and seven complete carcinomata were produced. The carcinomatous change was discovered between the 55th and the 360th day; in most of the cases it was found after the 150th day.

3. The hyperkeratotic pedunculated or sessile folliculoepitheliomata produced by irritation with coal-tar continued to grow after the irritant had been discontinued, and eventually developed into cutaneous horns. Some of these horns grew for a year after the withdrawal of the coal-tar, while others fell off spontaneously; in the great majority of the latter animals new cutaneous horns grew again from the same base, or from the neighbouring epithelium, as is the case in man.

4. The seventh and sixteenth cases of carcinoma in its early stage developed from cutaneous horns about 300 days after the tar had been discontinued.

5. The presence of metastasis was microscopically proved in the regional lymph nodes in the fourth and sixth cases of carcinoma.

6. The animals which bore folliculoepitheliomata did not begin to emaciate while the new growth maintained its benign character.

7. Yamagiwa's hypothesis (2) has been confirmed: The repetition or continuation of chronic irritation may cause a precancerous alteration in epithelium previously normal. If the irritant continue its action, carcinoma may be the outcome, even though no specific agent has been interpolated.

In conclusion, we desire to acknowledge our indebtedness to the Japanese Cancer Research Fund for its support in this work, to Dr. Mann and Dr. Horiuchi for their courtesy in correcting our English, and to Dr. Kikuta for the photographs and photomicrographs.

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EXPLANATION OF ABBREVIATIONS

Ab.c, Cystic abscess

C.d., Carcinomatous change in a folliculoepithelioma

Ch., Cartilaginous layer of rabbit's ear

D.ep., Dissociated epithelial cells

E.n., Network of carcinomatous epithelium

F., Fibromatous portion

F.c., Folliculoepithelioma carcinomatosum

F.n., Fibromatous nodule

I.ep., Infiltrative growth by carcinomatous epithelium

L., Lymphatic follicle

M.c.a., Metastatic accumulation of carcinoma cells

M.c.w., Metastàtic carcinoma cell layer on wall of cystic abscess

M.i.g., Metastatic carcinoma cells exhibiting infiltrative growth

M.l., Metastasis of carcinoma cells into lymph sinus in a lymph node

N.ep., Relatively normal epithelium

P.h., Perforation

Th.l., Thrombosis of lymph vessels caused by infiltrative growth of carcinomatous epithelium

Th.v., Thrombosis of vein caused by infiltrative growth of carcinomatous epithelium

R., Thickened wall of rodent ulcer

PLATE 1

FIG. 1. Multiple hyperkeratotic sessile folliculoepitheliomata on inner surface of ear on 204th day. Natural size.

FIG. 2. First case of cutaneous horn, on the 399th day after first application of coal-tar, and the 217th day after its withdrawal. Natural size.

FIG. 3. Second case of cutaneous horn, on the 422d day after first application of coal-tar, and the 217th day after its withdrawal. Natural size.

FIG. 4. Fourth case of carcinoma in its early stage; inner surface of ear, 165th day. Two-thirds natural size.

FIG. 5. Fourth case of carcinoma, on the 273d day after first application of coal-tar, and the 77th day after its withdrawal. Natural size.

FIG. 6. Secondary ulcer and central nodule on outer surface of ear; fourth case of carcinoma. This picture was taken on same day as figure 5. Natural size.

FIG. 7. Fourth case of carcinoma in its earliest stage, 118th day. Hematoxylin-eosin. Zeiss microplanar 35 mm.

FIG. 8. Fourteenth case of carcinoma in its early stage, 90th day. Hematoxylin-eosin. Zeiss microplanar 35 mm.

PATHOGENESIS OF CARCINOMA
KATSUSABURO YAMAGIWA AND KOICHI ICHIKAWA

PLATE 1

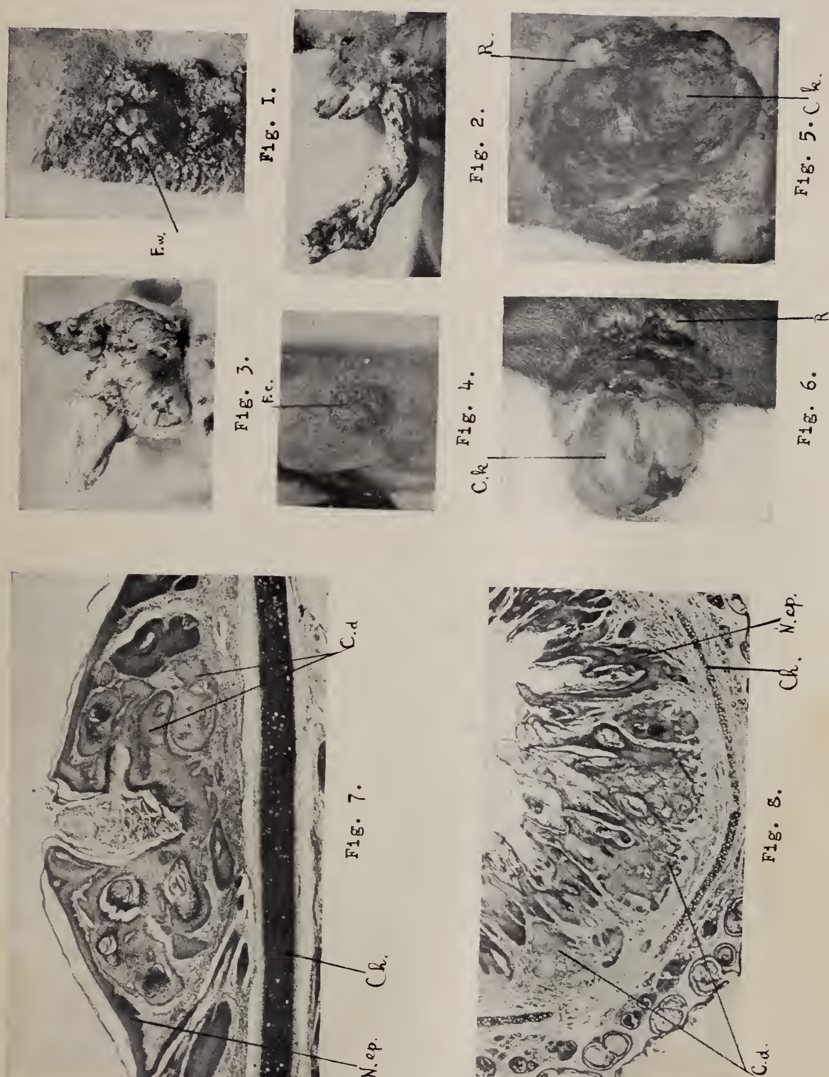

PLATE 2

Fig. 9. Thrombosis of vein by infiltrative growth of carcinomatous epithelium; thirteenth case of carcinoma in its early stage, 90th day. Hematoxylin-eosin. Zeiss projectionocular 2, obj. aa.

Fig. 10. Carcinomatous portion in fourth case of carcinoma in its early stage, 197th day. Notice dissociation of epithelial cells (D. ep.). Hematoxylin-eosin. Zeiss projectionocular 4, obj. aa.

Fig. 11. Second case of carcinoma (rodent ulcer), 103d day. Hematoxylin-eosin. Zeiss microplanar 35 mm.

Fig. 12. Third case of carcinoma, 151st day. Hematoxylin-eosin. Zeiss microplanar 50 mm.

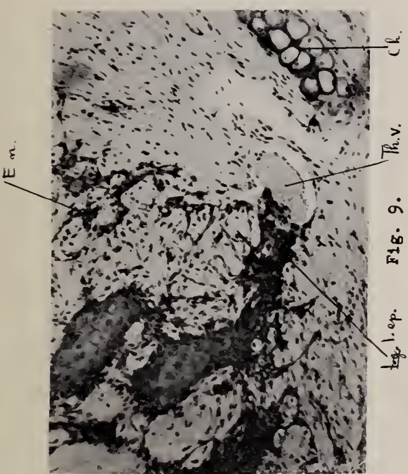

Fig. 9.

Fig. 10.

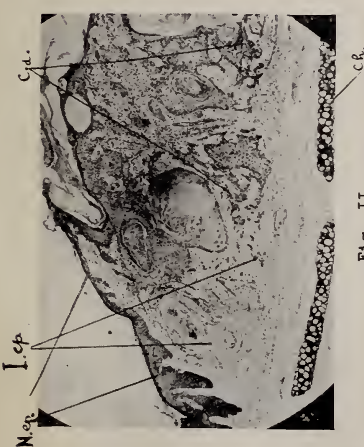

Fig. 11.

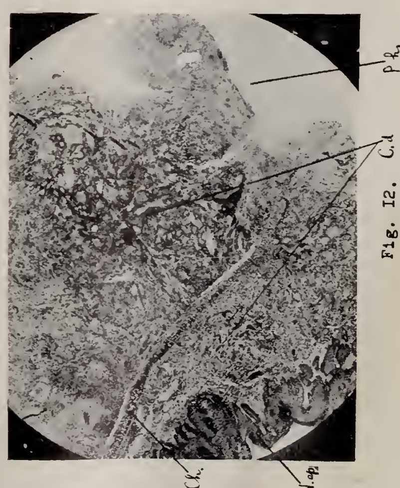

Fig. 12.

PLATE 3

Fig. 13. Fourth case of carcinoma in its early stage, 197th day. Hematoxylin-eosin. Zeiss, microplanar 50 mm.

Fig. 14. Fifth case of carcinoma, 120th day. Hematoxylin-eosin. Zeiss, projectionocular 2, obj. aa.

Fig. 15. Sixth case of carcinoma. Invasion of lymph channels at periphery of tumor. Hematoxylin-eosin. Zeiss, project. oc. 2, obj. aa.

Fig. 16. Seventh case of carcinoma, 565th day. Thrombi of cancer cells in lymph vessels. Hematoxylin-eosin. Zeiss, project. oc. 2, obj. aa.

Fig. 13.

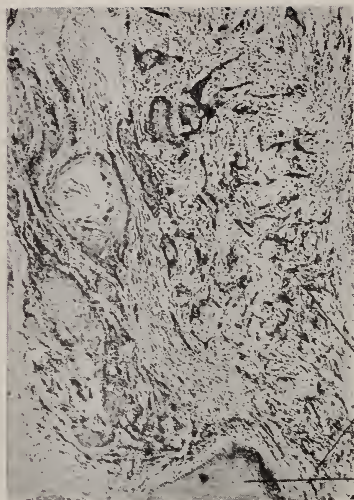

Fig. 14.

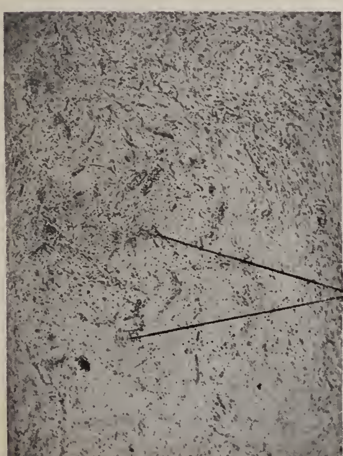

Fig. 15.

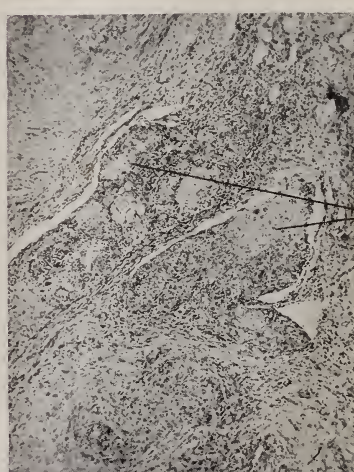

Fig. 16.

PLATE 4

FIG. 17. Metastasis in regional lymph nodes (fourth case). Hematoxylin-eosin. Zeiss project. oc. 4, obj. aa.

FIG. 18. Metastasis in regional lymph node (sixth case); cancer cells in lymph sinus. Hematoxylin-eosin. Zeiss project. oc. 2, obj. aa.

FIG. 19. Metastasis in regional lymph node (sixth case); stratified cancer cells cover the wall of a cystic abscess, which contains mucous fluid, degenerated epithelial cells, eosinophiles, and lymphocytes. Hematoxylin-eosin. Zeiss project. oc. 4, obj. aa.

FIG. 20. Metastasis in regional lymph node (fourth case). The metastatic cancer cells invaded the parotid gland, causing adhesion to the surrounding tissues. Hematoxylin-eosin. Zeiss microplanar 50 mm.

PLATE 4

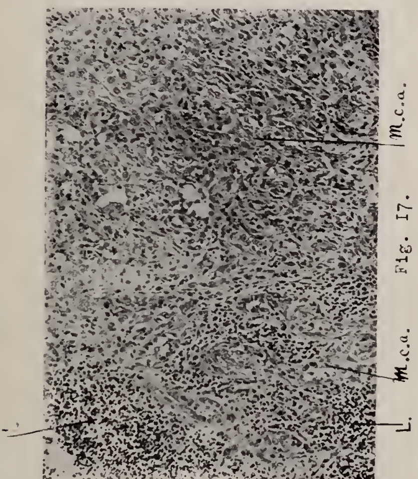

Fig. 17.

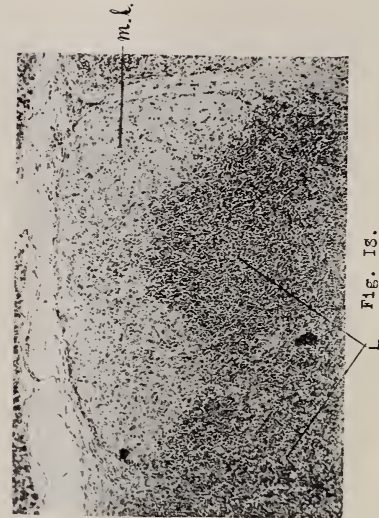

Fig. 18.

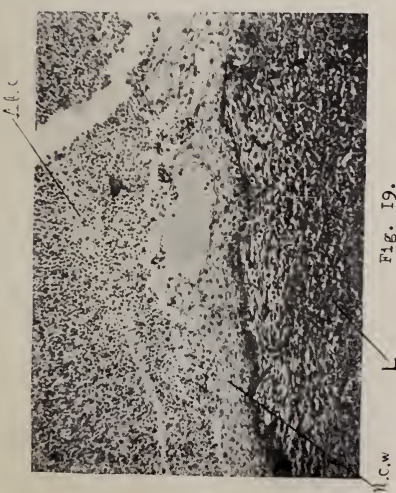

Fig. 19.

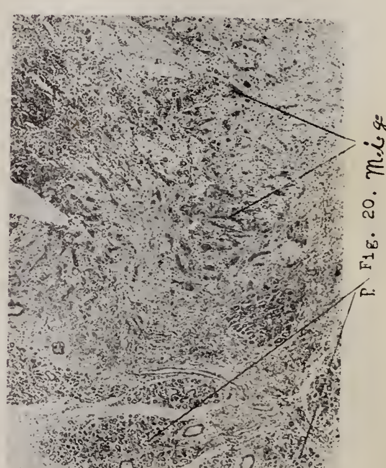

Fig. 20.

A HISTOLOGICAL STUDY OF HETEROLOGOUS TUMOR GRAFTS

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From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director

Received for publication, May 31, 1917

This paper records three series of experiments upon closely related factors in tumor immunity: (*a*) a study of the relation between the local tissue reaction and the heteroplastic tumor graft, (*b*) the effect of removal of the spleen upon the growth of heterologous tumor, (*c*) a study of the immunizing power of one heterologous tumor upon the growth of a second heterologous tumor of different type, and the possible influence of splenectomy upon such immunity.

The presence of lymphocytes, often in large numbers, in the tissues surrounding human tumors has long been observed by pathologists, many of whom have interpreted the condition as an effort on the part of the body to combat the growth of tumor cells. Da Fano (1), the first investigator definitely to correlate the presence of lymphocytes with the immunity to transplanted tumors, explained this immunity in terms of lymphocytic activity, the plasma cell, also, being considered as a factor. He offered no explanation regarding the manner in which these cells influence the growth of the tumor graft. Da Fano's suggestion has been supported by other investigators, and especially by Murphy (2), who has noted that the presence of large numbers of lymphocytes in the region of a tumor is frequently followed by cessation of growth, and believes that the two phenomena are causally related.

In a study of homeoplastic epithelial grafts, Leo Loeb (3) has expressed the additional view that the destruction of these grafts is partly due to the action of the lymphocytes which pene-

trate them and cause the death of their cells. This action is aided by the presence of dense fibrous material which grows into the grafts, separating them into small islands, and by continued growth gradually compressing and perhaps eventually destroying the cells. It is Loeb's opinion that these two agents may act either independently of each other, or together.

A study of heteroplastic tumor grafts of several different strains was undertaken in the hope of shedding some light on the histological relationship between the tumor and its surrounding leucocytes and connective tissue, and also to determine whether this relationship remains constant regardless of the strain of tumor used for the inoculations. Although Bashford and Russell, in an investigation similar to the one recorded in this paper, have ascribed the death of the graft to the cytotoxic and cytolytic action of the body juices, it is hardly probable that they would have their conclusions regarded as otherwise than purely inferential, as there is no form of cell degeneration characteristic of an attack by cytotoxins or cytolysins. Since a histological study shows the results rather than the cause of a degeneration, only the conditions of the tissues that may lead to the death of the graft and not the ultimate causes of cell death are considered in this paper.

Two carcinomata and two sarcomata were selected for the experiment. Of the carcinomata, mouse tumor 5 shows a rapid rate of growth in the mouse, in contrast to the very slow growth of mouse tumor 58, the other carcinoma employed. Mouse sarcoma 180 and rat sarcoma 7 proliferate rapidly in the mouse and the rat respectively; the former grows progressively, the latter regresses at a comparatively early period. These tumors were inoculated into the subcutaneous tissues by needle, in the usual dose of 0.003 gram.[1] From ten to fourteen days after inoculation, the grafts and their surrounding tissues were excised and submitted to microscopical examination (serial

[1] In previous publications from the Imperial Cancer Research Fund and from this laboratory, the inoculation dose, when the needle method is used, has been estimated as 0.01 or 0.02 gram; but such grafts have recently been found, as a matter of fact, to weigh about 0.002 and 0.003 gram respectively.

sections), attention being focused on the stroma reaction, the relative number of lymphocytes, the degree of fibrosis, the vascularity of the surrounding tissues, and the condition of the graft. The results of this examination are arranged and tabulated below (table 1).

Mouse carcinoma 5 was inoculated into 25 rats, and the grafts were removed on the twelfth and thirteenth days after inoculation. Upon removal, 68 per cent of the grafts of this tumor were degenerated. In the degenerated grafts, lymphocytic infiltration and fibrosis existed in about equal degree, though one or the other might predominate in the individual graft. In the grafts in which the tumor was growing, or in which the cells persisted in good histological condition (38 per cent), lymphocytes were scarce and fibrosis was almost absent. These results are capable of two interpretations; (*a*) either fibrosis and lymphocytic infiltration were preliminary to the death of the graft, or (*b*) fibrosis and lymphocytic infiltration was a replacement process, occurring after the death of the graft.

Mouse carcinoma 58 was inoculated into 14 rats, and the grafts were removed on the twelfth day after introduction. This tumor in foreign hosts calls forth a tissue reaction of very low grade, characterized by a relative scarcity of lymphocytes, a slight connective tissue response, and a poor blood supply to the surrounding tissues and the graft. While the histologically apparent causes leading up to the death of the graft may possibly be found in the presence of lymphocytes and the fibrous changes, slight though these reactions are, the scanty blood supply appears to be the more important factor. The study shows that a slowly growing tumor, when introduced into an alien host, causes a relatively slight response by the tissues of that animal, and that the fate of the graft is not determined simply by the relative number of lymphocytes and the degree of fibrosis.

Mouse sarcoma 180 was inoculated into 16 rats, the grafts being removed on the tenth and twelfth days of growth. Of the two growing tumors in this series, one was surrounded by but few lymphocytes, while the other was surrounded by a

large number of these elements. In several of the rats in which the tumors failed to grow, lymphocytes were few in number about the degenerated graft. In these animals, fibrous changes about the degenerated tumor were slight.

Rat sarcoma 7 was inoculated into 21 mice, the grafts being removed ten, thirteen, and fourteen days after inoculation. This tumor produces in twelve to fourteen days a very mild reaction, characterized by a small number of lymphocytes in the immediate neighborhood of the graft, and an absence, or only a slight grade, of fibrosis. The tissue about the graft was very vascular and generally edematous. About the blood-vessels in this tissue, at a distance from the graft, the lymphocytes were more abundant. It seems scarcely permissible to attribute the death of the graft to the action of the lymphocytes, unless it be conceived that the lymphocytes exert their lethal action at a distance. In one animal, in which the graft was much degenerated, showing but few surviving sarcoma cells, no lymphocytes could be detected in the tissues or in the immediate vicinity of the tumor. In the majority of the other animals, the extent of degeneration of the tumor cells can not be explained by the number of lymphoid cells, as they were few, even when degeneration was marked. Neither can death of the graft be referred to the activity of the fibrous tissue, for in cases where degeneration of the graft was extensive or even complete, fibrosis was absent or only beginning. A more plausible explanation of the death of the graft, based solely upon the microscopical picture and excluding cytolysis for the reasons given in another paragraph, is found in the disturbance of nutrition due to the edema of the tissues, and consequent interference with the blood supply.

In a further series of inoculations, the following results were obtained. Rat tumor 7, which was inoculated into 24 mice, produced at the end of fourteen days 5 growing tumors, the largest measuring 3 by 8 mm., and 9 degenerated tumors with surviving tumor cells. Mouse tumor 180 was inoculated into 109 young, and very young rats, and gave rise on the fourteenth day after inoculation to 9 tumors, the largest being 7 by 11 mm.

The same strain of tumor was inoculated into 200 older rats, of which 7 had tumors on the thirteenth day, the largest measuring 6 by 10 mm.; on the twenty-first day this tumor measured 5 by 7 mm. There was no evidence that young rats, two to six weeks old, offer a better soil for heteroplastic tumors than do animals three to five months old. The grafts did not grow so well in sick as in healthy animals.

The following conclusions may be drawn from this study. While the causes leading to death of heteroplastic grafts may, perhaps, be attributed to the combined action of lymphocytes and connective tissue, one or the other exerting the predominating action, they are not always determined by the number of lymphocytes or the degree of fibrosis. With certain tumors (sarcoma), death of the graft is not due to fibrosis and cannot be attributed to the lymphocytes, unless it be assumed that these cells act through a distance by the production of some toxic agent (cytolysin or cytotoxin) inimical to the tumor cells. Tumors introduced into animals of foreign species elicit at first a reaction of very much the same character as that produced in homologous animals. Ehrlich has shown that certain tumors survive for only about a week in the tissues of an animal of alien species and until recently this fact was held to be applicable to heterologous grafts in general. W. E. Bullock (4), however, has demonstrated that they can be kept alive in foreign tissues for nearly three weeks, and that if removed and transplanted into other animals of the same foreign species before regression sets in, can be propagated for several generations. Bullock's observation confirms a previous observation of Lewin (5), who was able to grow a rat sarcoma in a mouse for three weeks. Tumor strains show wide differences in the character of their growth in foreign hosts (see table 1), and Bullock's successful results may be explained by the choice of tumor used for the inoculation.

In another connection (6), we have demonstrated that removal of the spleen has no effect upon the fate of a homologous graft. Since the publication of that article, Murphy and Morton (2) have asserted that heterologous tumor grafts grow better

TABLE 1

TUMOR	STROMA REACTION	LYMPHOCYTES	FIBROSIS	VASCULARITY	CONDITION OF GRAFT
	per cent	*per cent*	*per cent*		*per cent*
Mouse carcinoma 5	Positive 32 Negative 68	Few 20 Moderate 48 Abundant 32	Absent 8 Slight 12 Moderate 56 Extensive 24	Moderate	Growing 16 Persistent 16 Degenerated 68
Mouse carcinoma 58	Positive 7 Negative 79 Negative? 14	Few 21 Moderate 79	Slight 86 Moderate 14	Poor	Growing 7 Degenerated 93
Mouse sarcoma 180	Positive 12 Positive? 6 Negative? 82	Few 19 Moderate 6 Abundant 75	Slight 25 Moderate 25 Extensive 50	Moderate	Growing 12 Degenerated 88
Rat sarcoma 7	Positive 28 Positive? 43 Negative? 29	Very few or none 62 Few 24 Moderate 14	Absent 67 Slight 33	Marked	Growing 28 Persistent 43 Degenerated 29

In classifying the stroma reaction as "positive" or "negative," it may be maintained that the time interval after inoculation is (10–14 days) in some animals long enough to permit a stroma reaction occurring and subsiding before examination. The truth of this possibility cannot be denied.

and survive for a longer period of time in animals which have been exposed to x-rays, attributing this to damaged lymphoid tissues. With the idea of impairing the lymphocytic processes of the body, the spleens were removed from 132 animals either before or after inoculation with alien cancer. One hundred and fifty-six normal animals served as controls. The tumors used were mouse carcinomata 5 and 58, mouse sarcoma 180, and rat sarcoma 7. From twelve to fourteen days after inoculation, the tumor grafts were removed and studied microscopically.

TABLE 2

TUMOR	NUMBER OF ANIMALS	TIME OF SPLEEN REMOVAL	GRAFT EXCISED IN DAYS	NUMBER OF TAKES	NUMBER SHOWING SURVIVING TUMOR CELLS	MAXIMUM SIZE OF TUMOR
5	7	6 days post inoculation	12	0	1	
5	30	Not removed	14	0	1	
58	22	5 and 6 days post inoculation	12 and 13	0	2	
58	19	Not removed	12	1	0	0.5 by 1 mm.
7	47	1 day before inoculation	12 and 13	0	10	
7	47	Not removed	12 and 13	0	6	
180	56	1 day before inoculation	10, 12 and 13	5	3	10 by 12 mm. on 12th day
180	60	Not removed	10, 12 and 13	2	0	3 by 4 mm. on 12th day

As shown in table 2, the spleen-free group gave a total of five growing tumors, and 16 growths more or less degenerated, but containing living tumor cells. In the control group, there were three growing nodules and seven degenerated ones with a few living cells. The growths averaged larger in the spleen-free than in the control animals, and the largest tumor (measuring 10 by 12 mm. on the twelfth day) was found in a spleen-free animal. Since these results are within the bounds of individual variations, it may be concluded that removal of the spleen has no appreciable influence upon the receptivity of an

animal for heteroplastic grafts, and that the growth of these grafts is not favored thereby.

Russell, Da Fano, and Bashford and Russell have shown that one inoculation of a heterologous tumor induces an immunity in the host toward a subsequent graft of the same strain of heterologous tumor. Bashford and Russell have specifically stated that this immunity is one directed against the foreign tumor merely as a foreign tissue and not in any sense as a neoplasm. We repeated these experiments, using splenectomized as well as normal animals, and various types of heterologous tumor for the second inoculation.

Twenty-one spleen-free and thirty-two control rats which had been inoculated with mouse tumor 180 (a sarcoma), and in which the tumors had disappeared, were reinoculated with mouse carcinoma 5. The results were negative.

Twenty-seven spleen-free and 34 control mice which bore no tumors after inoculation with rat sarcoma 7, were reinoculated twenty-one days later with the Flexner-Jobling carcinoma. No growing tumors were observed after eleven days, but a few of the grafts contained persisting cancer cells. Ninety-six rats inoculated with mouse sarcoma 180, 6 of which had tumors measuring 4 by 4 mm. or over, were reinoculated with the Ehrlich mouse sarcoma twenty-three days subsequent to the first inoculation. One had a growing tumor 6 by 9 mm. twelve days after inoculation and 4 by 6 mm. a week later. This tumor was found in an animal which had produced a growing tumor on the first inoculation with tumor 180. One hundred and eighty normal rats unsuccessfully inoculated with mouse sarcoma 180 were reinoculated with mouse sarcoma 37. Twenty-five bore tumors (see Chart 1) which in twelve days reached their maximum size and gradually receded thereafter; the largest tumor attained the size of 11 by 16 mm. The longest period of time in which cancer cells persisted in the tissues of an alien species was fifty-four days. This occurred after the inoculation of an emulsion of rat carcinoma 9 into a mouse. Figure 1 illustrates the persisting carcinoma cells; figures 2 and 3 show for comparison a larger field of tumor 9

taken from a stock series, and a section of mouse breast. It will be noted that the tumor cells are in better condition than the stroma, the latter showing marked hyaline degeneration.

Bashford and Russell, as a result of their investigations, consider immunity to heterologous tumors as a manifestation of immunity to a foreign tissue and not to tumor, and according to their view point, we should expect immunity to a second

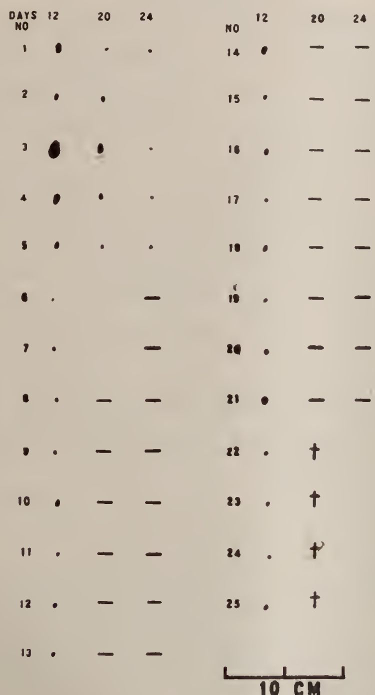

Chart 1

inoculation of heterologous tumor irrespective of the type of tumor used. The results of a second inoculation of heteroplastic tumor do, in fact, agree with the results recorded by the investigators quoted when sarcoma inoculation is followed by carcinoma inoculation, but they do not appear to harmonize when sarcoma inoculation is followed by sarcoma inoculation. Several explanations may be given for the diver-

gent results; they may be due to a difference in the growth energy of the two tumors at the time that they were used; or to a difficulty in producing an immunity against these sarcomata (7); or finally, it is possible that the dosage of the initial inoculation (0.003 gram) was insufficient to cause immunity against the second inoculation.

SUMMARY

While the death of some heteroplastic tumor grafts may, perhaps, be attributed to the action of lymphocytes and connective tissue, there is no histological proof that it is always determined by these factors.

Tumors elicit in foreign species a reaction of much the same character as that produced in homologous animals.

Removal of the spleen has no influence upon the receptivity of an animal toward heteroplastic tumor grafts.

Splenectomy does not favor the growth of heteroplastic tumor grafts.

One inoculation of a heterologous tumor does not always render an animal immune to the temporary growth of a subsequent heterologous graft.

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PLATE 1

Fig. 1. Graft of Rat Tumor 9, Persisting in Mouse Tissue for 54 Days. × 250

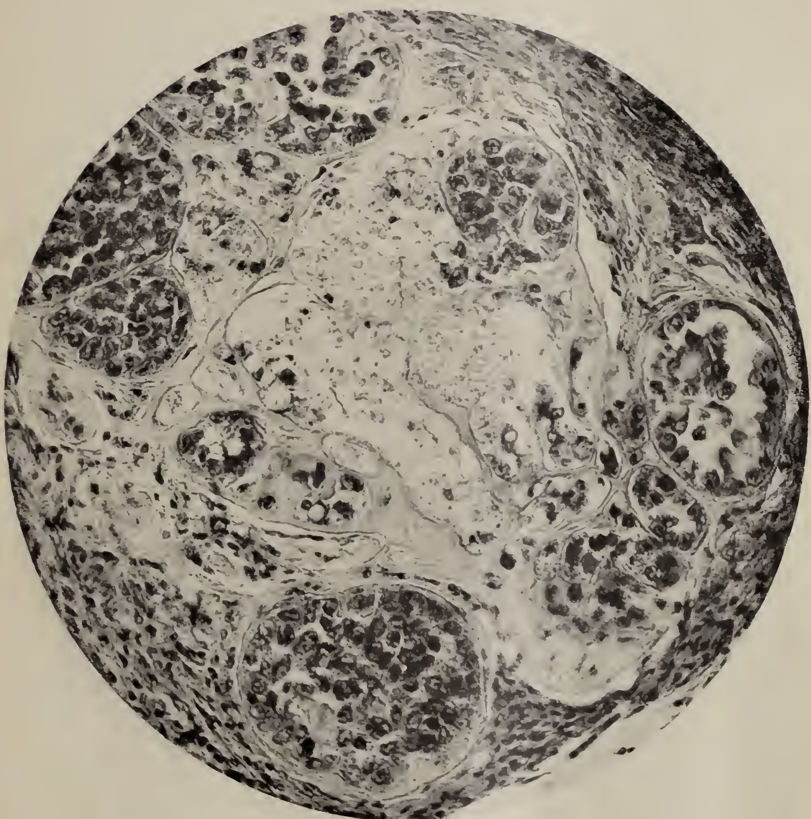


PLATE 2

Fig. 2. Normal Growth of Rat Tumor 9, for Comparison with Figure 1. $\times$ 250

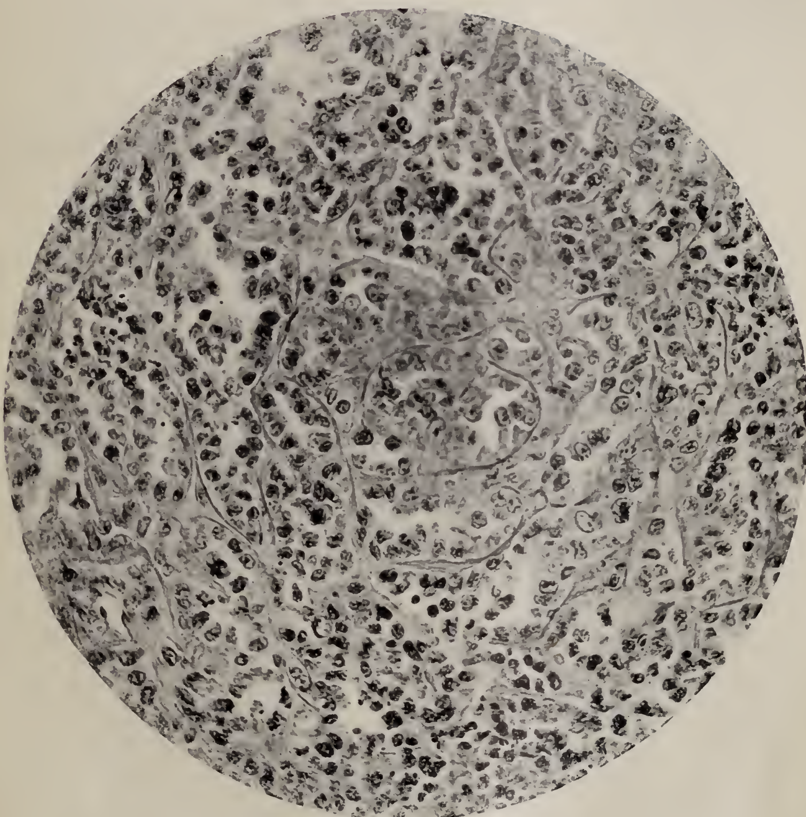
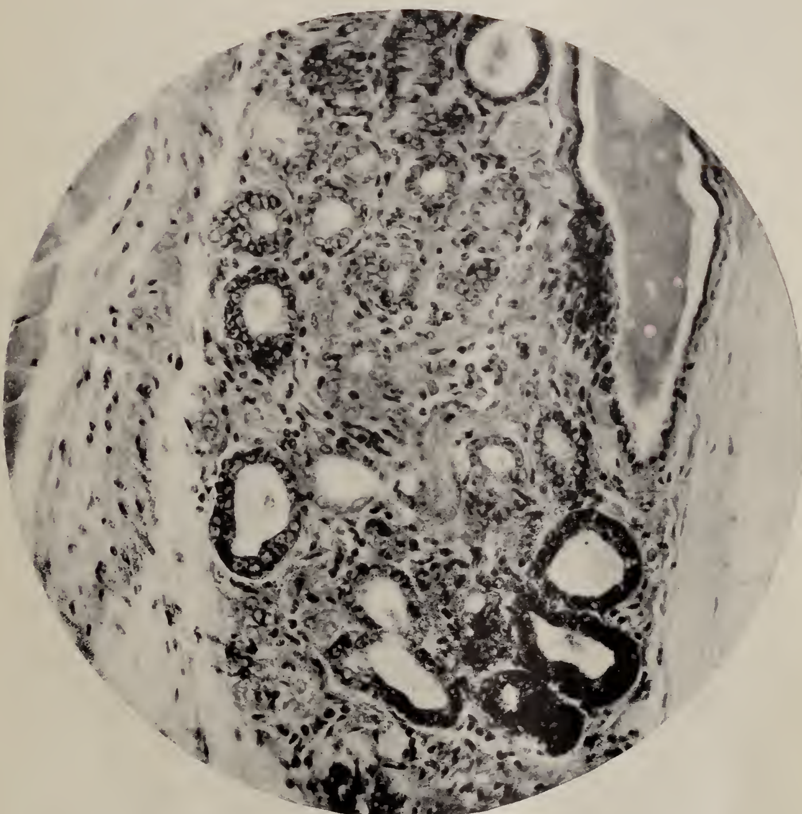


PLATE 3

Fig. 3. Normal Mouse Breast. $\times$ 250



SIGNIFICANCE OF THE CARTILAGE IN A CARCINO-CHONDROSARCOMA OF THE MOUSE

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A sarcomatous transformation of the stroma (1) in spontaneous and transplantable carcinomata of the mouse is not uncommon. In the rat, the cases are not so numerous, but this may be due only to the fact that comparatively few transplantable carcinomata have been found in this species; certainly its tissues are far from unlikely to give rise to sarcoma under the ordinary conditions of life to which these rodents are subjected, as is shown by the work of Bullock and Rohdenburg (2), and of other less recent authors. Whatever be the reason, the number of carcinosarcomata reported in the rat amounts to but three (3, 4, 5).

One such tumor has been discovered in the dog by Wells (6), and in man they are so extremely rare that up to 1908 Herxheimer (7) had been able to find only some twenty authentic cases in the entire literature, while six years later Saltykow (8) mentioned "about twenty-five," to which he added three more.

Although the transformation is regarded by most authorities as a sarcomatous change in the connective tissue framework of the tumor, this opinion is not yet universal, at least so far as neoplasms of the mouse are concerned. What these spindle cells actually are, and why they appear as they do in a few neoplasms, is an unsolved riddle, and one of the most important in pathology; for if they be sarcoma, then the unique opportunity has been given of observing the neoplastic process from its very inception.

Most of the authorities who regard the alteration in question as a true sarcomatous change, suggest that it arises in obedience

to some special sort of stimulation exerted upon the stroma by the epithelial portion of the tumor, though what the nature of the exciting agent may be is not even suspected; some refer to it vaguely as chemical, and there are not wanting those who would attribute the alteration to a parasite living in symbiosis with the carcinoma cell. The hypothesis that the stroma becomes sarcomatous in consequence of repeated transplantation was seen to be untenable as soon as the transformation was discovered in a spontaneous tumor (9), while the suggestion that the cellular connective tissue between the alveoli is merely granulation tissue fell to the ground with the demonstration that it can be transplanted (10).

Still other explanations have been advanced in elucidation of the sarcomatous change. Thus Ribbert (11) asserts that no irritation by the parenchyma would elicit sarcomatous transformation unless the stroma were especially susceptible to it; now since the transplantable tumors of the mouse, he believes, are not true carcinomata at all, but rather a species of neoplasm allied to the cylindromata, they must have a stroma which properly belongs to them, or in other words, one springing from a connective tissue embryonal remnant displaced coincidently with that other one which gives rise to the epithelial portion of the growth; this stroma, transplanted with the parenchyma at each inoculation, becomes continually more independent until finally it develops into sarcoma. His hypothesis of a mixed epithelial and connective tissue embryonal remnant, he thinks, will probably best explain carcinoma sarcomatodes in the human subject also, some unknown influence taking the place of transplantation in inciting to malignant proliferation a stroma already so predisposed.

All the hypotheses so far discussed have this much, at least, in common, that all concede the spindle-shaped cells between the alveoli to be derivatives of the connective tissue. A few observers, however, and notably Krompecher (12), deny any such origin, and insist that these are epithelial elements which have assumed a spindle shape; other writers, it is true, have suggested such a change in morphology as an alternative hypo-

thesis, but none has espoused it so warmly as Krompecher. His view, which he bases upon the zoölogical investigations of others as well as upon his own oncological research, may be summarized as follows: A direct transformation of epithelium into connective tissue takes place normally in the embryo and among the lower vertebrates. The conditions necessary for this change are a heightened proliferative activity in the epithelium and an appropriate plasticity in the stroma, both of which exist not only in the embryo and the lower vertebrates, but in carcinomata with "hyaloid" or myxomatous stroma. Under such circumstances, the epithelium becomes frayed out until its cells resemble exactly those of the connective tissue, as to both nucleus and protoplasm. Furthermore, collagen fibrils have been demonstrated in epithelial cells that have assumed the spindle shape, and even the production of cartilage by ectoderm has been described by several writers.

If, continues Krompecher, epithelium can be transformed into connective tissue, as all these observations appear to imply, it is difficult to refute the hypothesis that in carcinosarcomata the sarcomatous portion develops from the carcinomatous; and he terminates his article with the conclusion that while epithelium is ordinarily evolved from epithelium, and connective tissue from connective tissue, the direct metaplasia of epithelium into connective tissue (or of carcinoma into sarcoma) cannot be gainsaid, and, indeed, under suitable conditions, is not rare. Few pathologists are willing, however, to transfer to adult human cells the findings of the embryologist and the zoölogist, at least until further experience has demonstrated that a parallel may safely be drawn.

That there does occur in the mouse a type of new growth in which the epithelium assumes a spindle shape, can scarcely be denied. Apolant (13) has described a transplantable tumor of this sort, and three similar spontaneous neoplasms have come under the writer's observation at the Crocker Fund, two of which are here reproduced. Still, this may not be the whole story. It will be observed from figures 1, 2, and 3 that the transition to the spindle shape is gradual, and from figure 4

(it is not so in all such tumors) that the change has occurred toward the center of the alveoli; quite the opposite appearance characterizes the condition ordinarily believed to represent a sarcomatous transformation of the stroma, the line of demarcation being there abrupt and the spindle cells lying outside the alveoli, from which they are often separated, indeed, by characteristic halos of clear cells (14). All this suggests that there are two distinct varieties of tumor containing spindle cells, one (pure carcinoma) in which these elements are of epithelial, and another (carcinosarcoma) in which they are of connective tissue origin. Yet morphological evidence is, after all, apt to be misleading, and it is fortunate that other proofs in favor of this view are not lacking.

It is the province of this communication to offer certain new observations in favor of the hypothesis that the spindle-shaped cells in the type of growth ordinarily called carcinosarcoma are actually of connective tissue origin; it must nevertheless be admitted at once that the evidence is not actually conclusive, though it may be regarded as highly suggestive unless one wishes to assume, with Krompecher, that epithelium may be able to produce connective tissue elements.

In a transplantable mouse carcinoma (no. 48), which possessed temporarily the power to produce the sarcomatous transformation in its stroma, cartilage[1] (fig. 5) was discovered in at least three of the four mixed growths in the second generation (2A); as only a very small piece of the fourth tumor was available for examination, it cannot be said definitely that this growth contained no cartilage. The three tumors were 75, 177, and 205 days old respectively, while that one in which it was not found was 76 days of age. Cartilage appeared once more, in a 53-day old growth of the third generation.

The readiest explanation of such a finding is, of course, that a portion of costal cartilage had become involved by the tumor during its growth, and had been removed with it. Serial sections, however, proved conclusively that this was not the case; many independent islands of cartilage, some composed of only

[1] Kaufmann (Lehrbuch Path. Anat., Berlin, 1911, ii, 1089) has reported, as a unique finding, a chondrosarcocarcinoma of the mamma in the human subject.

a few cells (fig. 6), lay scattered about through the stroma, and, furthermore, there was a very gradual transition between these cartilaginous areas and the surrounding sarcoma (fig. 7). No course remains open, therefore, but to regard this cartilage as a product of the spindle-shaped cells surrounding it.

The question immediately arises, then: What sort of cells were these? Krompecher (15) quotes observations by a number of investigators which seem to suggest that products of the various germinal layers cannot be sharply distinguished one from the other, and especially germane to the present article is the production of cartilage by the ectoderm, a process which has been observed by Platt and others. But, as Krompecher himself points out, the transformation of one type of tissue into another, and particularly of epithelium into connective tissue, cannot be directly proved in postembryonal life; here the problem can be solved only indirectly by the study of transitional stages and by the help of analogy.

Since it is not definitely known whether or not epithelium which has once matured can produce cartilage, and since, on the contrary, it is known that connective tissue tumors are able to form cartilage, it seems safer to assume, at least for the present, that any neoplasm which has produced cartilage must have contained connective tissue elements. If this hypothesis be sound, then the spindle cells in tumor 48, and probably those also in other neoplasms of its class, were of connective tissue derivation, and the name carcinosarcoma is justified.

Evidence somewhat resembling that offered in the present paper has been adduced by Haaland (16), who discovered intra- and intercellular fibrils in the sarcomatous parts of mixed neoplasms, and, more recently, also, by Slye, Holmes, and Wells (17), who regard the presence of myxomatous degeneration in one of their tumors which resembled the mixed growths, as suggestive of sarcoma.

As cartilage was never found in the stroma of pure carcinomata in tumor 48, it is obvious that interpolation of the sarcomatous transformation was one of the conditions necessary for the emergence of this metaplasia. What the others were, however, it is impossible to say. The fact that the connective tis-

sues of three mice, all of one breed, showed cartilaginous differentiation, makes it impossible to dismiss, as a second factor, some such predisposition to cartilaginous metaplasia in this strain as characterizes, for example, the dog's mamma, though the explanation may be regarded as improbable. The reappearance of cartilage in the following (third) generation, in a mouse of different breed, is deprived of any significance by the fact that this generation (3A) was transplanted from that (2A) in which the cartilage arose; the existence of cartilage in it, therefore, may have been due merely to the transplantation from the preceding generation of sarcoma cells able to differentiate in this direction. A third factor, and the only remaining common one, was the presence of carcinoma 48, the parenchyma of which seems to have had the power not only to bring about the sarcomatous change, but to determine differentiation into cartilage in the sarcoma so educed. If this neoplasm ever regains the power to induce sarcoma, it will appear, without much doubt, that the emergence of cartilage is associated with the parenchyma rather than with the soil, since it is already known that the carcinomata exert other influences, quite as remarkable, upon their stromas.

It seems more probable that the cartilage emerged by differentiation of the connective tissues, than that embryonal remnants of cartilage were present; for while the connective tissues of the mouse may, perhaps, contain embryonal rests, misplaced when the various cartilages were laid down and potentially able to form cartilage under pressure of a suitable agent such as the parenchyma of carcinoma 48 appears to have been, their existence has not been proved. In favor of the differentiation hypothesis, on the other hand, stands the fact, already known, that certain carcinomata in man cause the production of bone in their stroma, while certain other ones in the mouse compel the elaboration of a highly vascular connective tissue scaffolding. If bone or blood-vessels, it may well be asked, why not cartilage?

Hence the preferable explanation of the occurrence of cartilage in tumor 48 is to ascribe to the parenchyma of this neo-

plasm the power to determine cartilaginous differentiation in a sarcomatous stroma. A similar hypothesis has been advanced in the description of a spontaneous chondroosteosarcoma of the mouse mamma by Murray (18), who, like the present writer, regards as unnecessary the assumption of a congenital foundation for the presence of cartilage in spontaneous mammary tumors, preferring to ascribe it to postnatal differentiation.

SUMMARY

The presence of cartilage in the sarcomatous portion of a carcinosarcoma in the mouse strongly suggests that the sarcomatous part was of connective tissue, rather than of epithelial origin.

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PLATE 1

FIG. 1. SPONTANEOUS MOUSE CARCINOMA $\left(\frac{646}{0}\right)$ WITH SPINDLE EPITHELIUM. $\times$ 250

PLATE 1

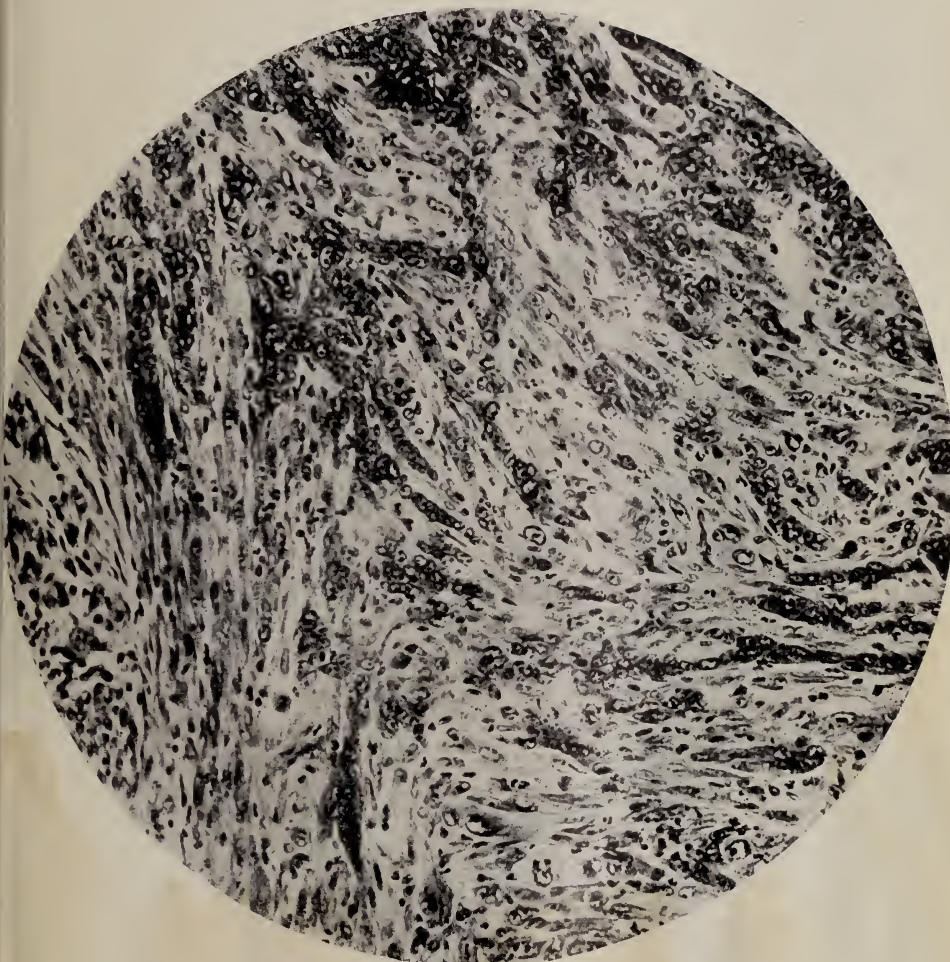

PLATE 2

FIG. 2. SPONTANEOUS MOUSE CARCINOMA $\left(\frac{936}{0}\right)$ WITH SPINDLE EPITHELIUM. $\times$ 250

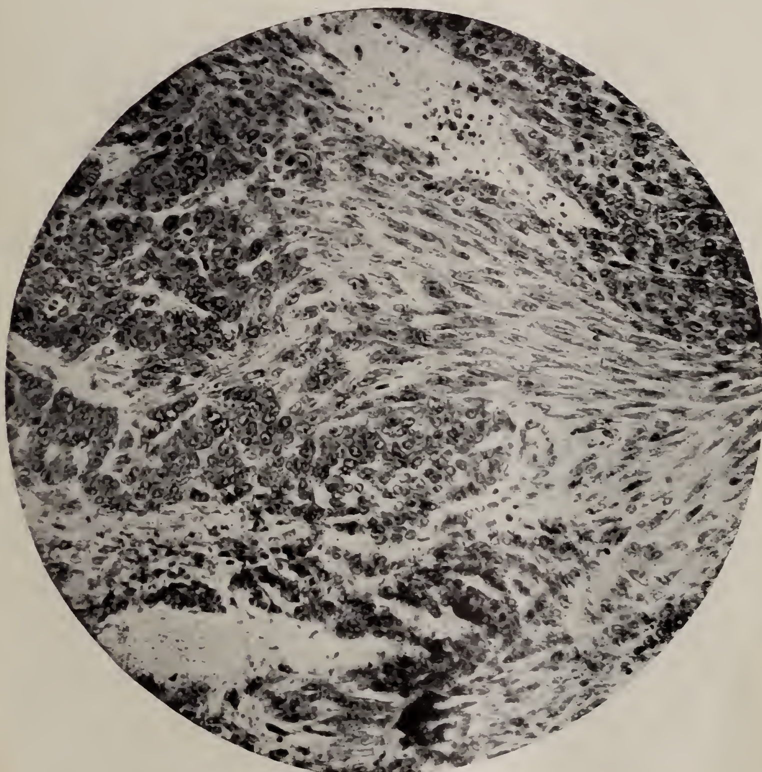

PLATE 3

FIG. 3. HIGH POWER VIEW OF CENTRAL PORTION OF FIGURE 2. $\times$ 480

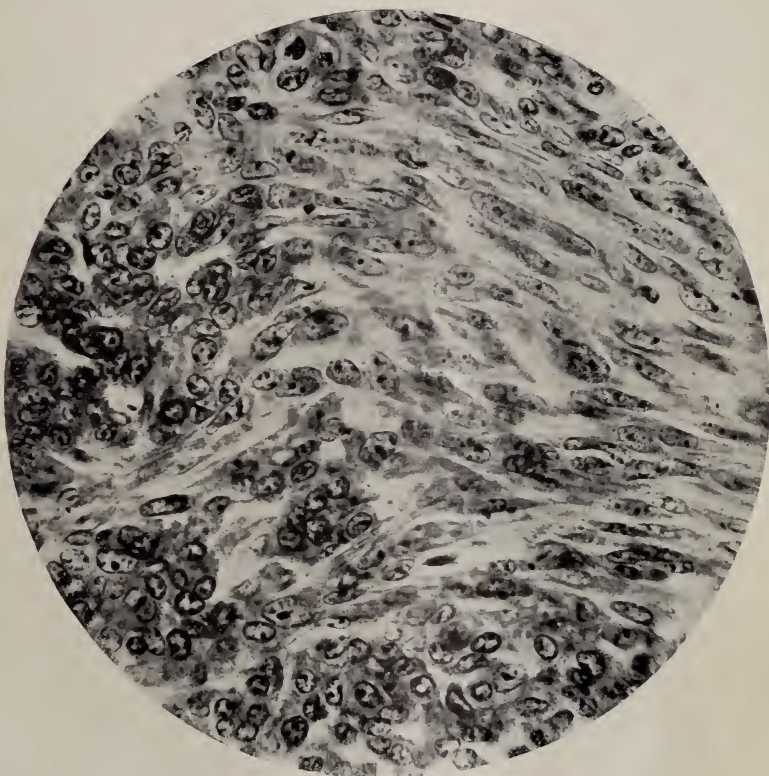

PLATE 4

FIG. 4. SPONTANEOUS MOUSE CARCINOMA $\left(\frac{636}{0}\right)$ WITH SPINDLE EPITHELIUM $\times$ 80

FIG. 5. TUMOR 48. CARTILAGE IN A MIXED 205-DAY OLD GROWTH OF THE SECOND (2A) GENERATION. $\times$ 75

FIG. 6. SMALL ISLAND OF YOUNG CARTILAGE IN SECOND GENERATION (2A) TUMOR 48. $\times$ 400

FIG. 7. GRADUAL TRANSITION BETWEEN SARCOMA AND CARTILAGE IN SECOND (2A) GENERATION OF TUMOR 48. $\times$ 150

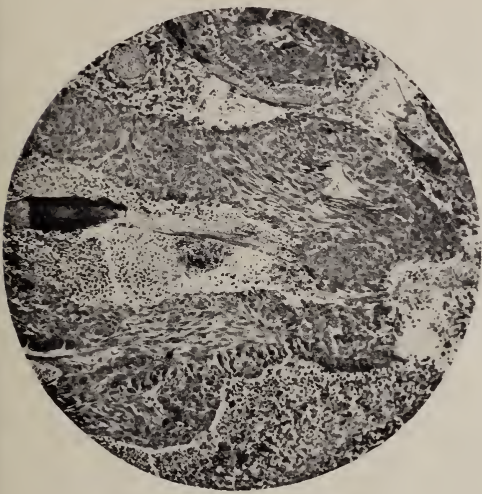

Fig. 4

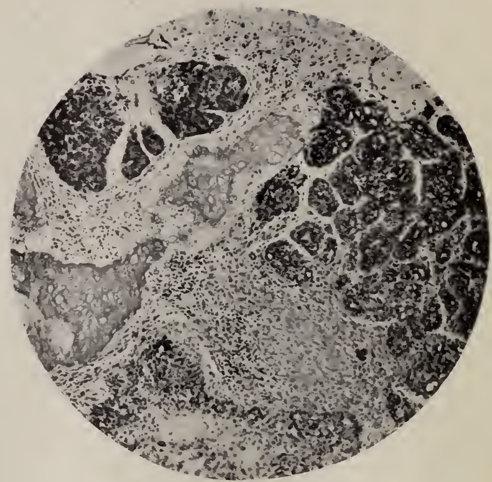

Fig. 5

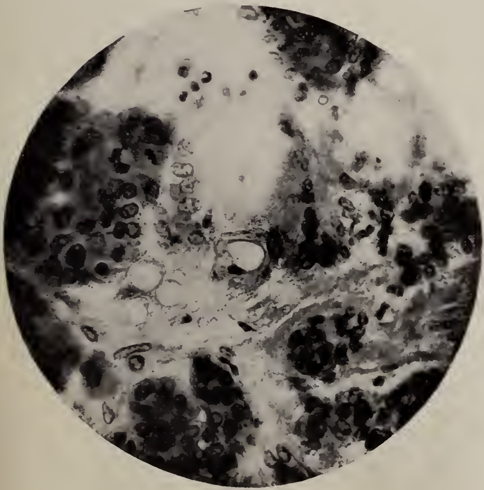

Fig. 6

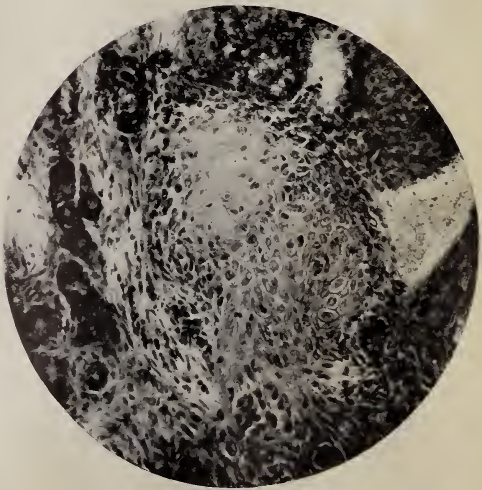

Fig. 7

GROWTH OF TUMORS IN THE CHICK EMBRYO

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When Murphy (1) introduced the chick embryo as a soil for the growth of foreign tissues, it appeared that it might prove to be a medium for the growth of human neoplasms as well as for the transplantable tumors of animals, offering thus a wide field for investigation. This report presents the results of experiments that were undertaken to determine any differences that may occur between tumor growth in the original species and in the chick embryo.

The problem was divided into three parts. The first dealt with the results obtained with tumors of different growth rates, though it included, also, a study of the general characteristics of tumors growing in the chick embryo and the results obtained with human tumors inoculated into this medium. The second problem was a comparison between early stages of tumor grafts in the chick and in the original species. The third dealt with the effect of prolonged residence in the chick upon the growth of a mouse tumor therein, and its behavior when returned to the animal.

In the experiments undertaken the eggs employed were obtained from one dealer, but were not all from the same breed of fowl. It does not seem likely, however, that a difference of breed would have an influence on the growth of tumors from a different class of animal. The eggs were incubated at 39.4°C. and inoculations were made on the fifth to the eighth day of incubation, the eggs having been previously candled and the location of the embryo marked. The technique of the inoculation, similar to that described by Peebles (2) and later developed

by Murphy (1), was as follows: With a small knife a square of about 7 mm. was cut in the shell and carefully removed. The vitelline membrane was then torn with sterile forceps and the tumor graft inoculated with a pair of curved forceps through this opening upon the underlying allantois. The fragment of shell was then replaced and sealed with paraffin. After inoculation, the eggs were returned to the incubator and kept there until the seventeenth or eighteenth day of incubation, when they were removed and examined for the graft.

It was found that about 35 per cent of the embryos survived the operation. The number bearing tumors varied with the growth used and also with the series. For example, with the Ehrlich sarcoma the number of takes was usually between 70 and 80 per cent, while with the Crocker mouse carcinoma 11 only about 50 per cent of takes were found. From this it is seen that tumors grow in the membranes of about 30 per cent of the total number of eggs used.

GROWTH RATE

The time factor is of the greatest importance for tumors growing in the egg. In animals many transplantable tumors do not appear until two or three weeks after inoculation, and occasionally even longer; now when one considers that a tumor has at most thirteen days, and usually less (Murphy (3)), to grow in the chick embryo, it is obvious that unless slowly growing tumors proliferate much more rapidly here than in the animal, only a very small nodule, or none at all, will be found at the conclusion of this period. The time factor is especially concerned where the attempt is made to grow human tumors in the egg, for these increase in size even more slowly than transplantable animal tumors.

In the experiments undertaken to discover what bearing growth rate in the animal has upon tumor growth in the chick embryo, six transplantable tumors were used. These included three mouse tumors, the Ehrlich sarcoma, the Crocker carcinoma 11, and the Twort carcinoma; two rat tumors, the Im-

perial Cancer Research Fund carcinoma 9 and sarcoma 16; and one guinea-pig sarcoma, Crocker 1.

In the animal, the Ehrlich sarcoma and carcinoma 11 are tumors of rapid growth, usually giving rise to a nodule the size of a pea within a week; the latter, however, grows somewhat more slowly than the former. The Twort carcinoma grows more slowly than no. 11, and does not generally appear until the third week. The two rat tumors are both slow-growing, but of slightly different characteristics; sarcoma 16 appears usually by the third week and enlarges fairly rapidly, while rat carcinoma 9 often appears by the second week, but enlarges more slowly. The Crocker guinea-pig tumor 1 is a fibrosarcoma that appeared in the first generation only after six to eight months, and in later series after three months or more. These characteristics are, of course, general and subject to variation, but they give a fair idea of the growth rate of these tumors in the animal body.

The tumors were inoculated into series of eggs in uniform dosage—approximately 0.003 gram in each instance. It was impossible to inoculate all the tumors at once, but the factors of soil, temperature, and technique were not varied throughout the experiment.

The following series of experiments has been chosen at random from among many others, all of which gave the same result.

Of 36 eggs inoculated with the Ehrlich sarcoma, 8 were alive when opened ten days later, and of these 4 bore tumors. The grafts had grown well and averaged 5 mm. in diameter, being almost spherical in shape. Microscopically, they exhibited the characteristics of the Ehrlich sarcoma in a healthy growing condition.

Carcinoma 11 was inoculated into 32 eggs in a similar way. Nine days later, 7 of the eggs were found with living embryos, of which 5 bore tumors. These growths averaged between 3 and 4 mm. in diameter, were generally spherical in shape, and showed microscopically the characteristics of this tumor when in a healthy growing condition.

The Twort mouse carcinoma was inoculated into 63 eggs.

Ten days later 6 eggs were found to contain living embryos, and of these 3 had small areas on the membranes, not more than 2 mm. in diameter. These areas were not spherical but flat, and it was difficult to tell by the naked eye whether or not they were composed of growing tissue. Microscopic examination proved, however, that all three areas contained healthy growing tumor.

Rat carcinoma 9 was inoculated into 53 eggs in the usual way. Ten days later the eggs were opened, and 15 living embryos were found, of which 6 bore what were evidently grafts. The largest of these was 6 mm. in diameter and 2 mm. in thickness; the others were about 3 mm. in diameter, not spherical but flat, and less than 2 mm. thick. Sections showed all the areas to contain healthy growing tumor.

Rat sarcoma 16 was inoculated into 23 eggs. Ten days later the eggs were opened and 5 were found to contain living embryos. Of these 2 showed small translucent areas on the membranes, one 1.5 mm. in diameter and the other 1 mm. in diameter. Both were only slightly elevated. On section they were proved to contain growing tumor tissue.

With the Crocker guinea-pig sarcoma 1, 57 eggs were inoculated in the usual way. Ten days later there were discovered 7 areas which appeared to be thickenings of the membrane. One of these on section showed the presence of a few tumor cells which, although evidently living, showed no signs of growth.

These experiments clearly demonstrate that the growth rate of a tumor in animals is an important factor in determining the size which the growth will attain in the chick embryo. With the two tumors which grow rapidly, the Ehrlich sarcoma and carcinoma 11, good sized tumors resulted in the chick. With the three tumors that grow more slowly in the animal, Twort, rat 9, and rat 16, much smaller growths resulted in the chick with the same dosage, in the same time and under similar conditions. The outcome with the guinea-pig sarcoma, the most slowly growing of all, in the animal, is even more distinct in this respect than in the case of any of the other tumors. This tumor gave no growth at all in the chick, although several series of inoculations were made.

In the discussion of these results some points of interest may be brought up. The first is, that tumors growing in the chick embryo preserve approximately the same growth rate that they exhibit in the original animal. This has an important bearing upon the use of the chick as a soil, because, for experiments that must continue for more than one generation, this medium becomes limited to the more rapidly growing tumors. Its limitations as a culture medium become even more obvious when one considers that of the fertile eggs inoculated, less than 30 per cent bear tumors, and that the resulting grafts are so small in the case of slowly growing tumors, that by the second generation a sufficiently large number of eggs could not be inoculated. The result would be that after a few generations the experiment would be automatically terminated by lack of tumor.

Another interesting finding is that the chick embryo is not a more favorable growth medium for the animal tumors than the healthy animal in which it is native. If it were, one might expect to see the slowly growing tumors much larger than they are in the animal within the given time. This is not the case, however, for they appear to attain in the chick about the same size that they do in the animal after proliferating for an equal period. This apparently eliminates any possibility of stimulation or of retardation of the growth in the chick, so far as the methods employed can determine.

During the foregoing experiments, many microscopical features were noted, which may be of interest here. In general one may say that tumors growing in the chick embryo retain the structure which characterizes them in the animal, except that their stroma is now derived from the chick.

Sarcoma cells are seen growing out singly from the graft, and mesenchyme cells and blood-vessels from the chick penetrate it. The sarcoma cells appear to be larger, but this is probably due to the lower tissue pressure in the chick; that is, the tissue is looser and the cell has more space in which to expand. Many mitotic figures in all stages of division are present throughout the tumor.

The carcinomata preserve the alveolar or glandular arrange-

ment and their cellular elements have the same appearance as in the animal. Between the groups of tumor cells extend the connective tissue and blood-vessels of the chick. The carcinoma cells do not appear so definitely enlarged as those of the sarcomata, mainly because they retain their group formation and are consequently crowded by one another. Near the edge, where at times they may be seen extending outward in groups of two or three, they are apt to appear larger than towards the center of the tumor graft. Mitoses are not quite so frequent as they are in the sarcomata, but are nevertheless numerous.

A biological characteristic of considerable importance is the preservation in the chick of the angioblastic tendencies of a tumor, one instance of which seems especially worth recording. Carcinoma 11 was originally a hemorrhagic growth, and this characteristic reappears occasionally in its routine passage through mice. Such a neoplasm contains large areas of hemorrhage, as well as hemorrhagic cysts, and these features characterized one of the nodules which developed in the chick after inoculation with tumor 11. The spaces, however, were, of course, filled with chick blood corpuscles, and the walls of the spaces composed of chick connective tissue and, so far as could be determined, lined by chick endothelium.

The reaction on the part of the connective tissue and wandering cells around the tumors growing in the chick embryo varies somewhat with each graft. The connective tissue reaction at times is dense, but usually it is delicate and quite typical of embryonic connective tissue. As for the wandering cells, there may be few or many. In some sections, they gather in groups around the blood-vessels. These cells, practically all of which were of the myeloid or granular leucocyte series, were present around all the tumor grafts, the only variation being found in the number present.

HUMAN TUMORS IN THE CHICK EMBRYO

Although the results following the inoculation of human tumors into the chick embryo were not entirely conclusive, it seems advisable to record them in this connection. The

material was obtained as fresh as possible from a hospital nearby, and the inoculations were made in the customary way. The dose was 0.003 gram. It was found impossible always to have eggs at the same age for each tumor, but they were used on, or near, the seventh day of incubation. Eight human tumors, and a metastatic nodule from one of them were inoculated into 350 fertile eggs. The following types of neoplasm were employed: Scirrhous carcinoma of the breast; medullary carcinoma of the breast (two); metastasis from a medullary carcinoma of the breast; squamous-cell carcinoma of the leg; adenocarcinoma of the breast (two); carcinoma of the testicle; chorioepithelioma of the uterus.

No growth resulted from these inoculations; in a few sections, cells that were evidently those of the human tumor introduced were found, but these were often multinucleated and showed no evidence of mitoses. These cells, therefore, were probably not growing, although the possibility that they might have begun to proliferate at some later time is not to be lost sight of.

The spontaneous tumors of mice resemble human tumors more closely than the transplantable ones and it may be of interest to mention here the results obtained with them. A few spontaneous mouse tumors were inoculated into eggs; some of these grew and some did not. The tumors resulting from those that grew were small and gave little promise of prolonged propagation in the chick embryo.

COMPARISON OF EARLY STAGES

In order to determine what difference might occur between the progressive growth of a tumor in the chick embryo and in its original species, a study was made of growing tumors in their early stages in the chick.

Two growths were used, the Ehrlich mouse sarcoma, and the Crocker mouse carcinoma 11, and the technique of inoculation was similar to that used in the other experiments. Tumor to the amount of 0.003 gram was inoculated into each egg on the seventh day of incubation, and the grafts removed at each period and serial sections cut of each graft.

The Ehrlich sarcoma, after twenty-four hours' residence on the chick membranes, showed signs of beginning growth. At the periphery of the graft, the tumor cells appeared to be extending out to a slight degree into the chick mesenchyme. The cells towards the center of the graft, however, showed signs of necrosis, and the stroma also was becoming necrotic. At the periphery of the graft, the mesenchyme was sending delicate filaments between the tumor cells. At the end of forty-eight hours, the process of organization of the tumor had progressed much farther. The cells had migrated some distance from the graft, and the mesenchyme and capillaries of the chick had extended toward the center of the tumor. The tumor cells at the periphery were sending out long filaments which extended into the chick tissue, and also connected one cell to another by more or less prominent bridges. The impression was given that these elements at the border formed a syncytium, but this was probably not the case, for it was possible occasionally to make out a cell membrane in some of the border processes. At the end of the third day, the organization of the graft was usually complete. The capillaries and new stroma formed by the chick tissue were seen throughout the tumor. The necrotic tissue at the center of the graft had been replaced, and the tumor had distinctly enlarged. The later stages were merely a continuation of the process described above. Mitotic figures were numerous in the tumor cells and a certain number of wandering cells were always present.

A study of the preparations of tumor 11 showed the process to be similar in general to that described for the Ehrlich sarcoma. The central necrosis was present and the growth of the tumor and of the reacting chick tissues occurred at the same time that they did with the sarcoma. Those acini at the periphery which remained healthy were completely supplied with stroma and capillaries by the end of the second day. The later stages showed the organization of the area of central necrosis. It is interesting to note that, as this area of central necrosis became organized, the tumor acini grew back into it, following the new tissue until the tumor was uniform throughout. This complete

organization is usually seen by the end of the fourth day. Here also, wandering cells were numerous and the tumor cells contained many mitotic figures.

No material difference has been noted between the manner in which these tumors established themselves in the chick and in the mouse. The chick tissues seem to supply the framework necessary for growth just as efficiently as the animal does. One difference, however, is to be noted; the process is apparently completed in the chick in much less time.

THE EFFECT OF PROLONGED RESIDENCE IN THE CHICK

In a previous communication (4) it was pointed out that the Ehrlich sarcoma, after growth in the chick embryo, shows evidence, on its return to mice, of impaired growth power. After one generation (ten days) in the chick, the number of takes in mice and the size of the tumors were both less than in the control series. After two generations in the chick, or twenty days, the number of takes was still less and the resulting tumors even smaller. It was also pointed out that these growths regained their normal growth rate and percentage of takes when they were transplanted back into mice. Upon repeating these experiments, identical results were obtained; but it was also observed that this sarcoma, after growing continuously in the chick for two generations, contained areas of necrosis, a rare finding among neoplasms grown in this medium.

These results all indicated a distinctly unfavorable effect upon tumors proliferating in the chick embryo, and it was of interest to discover whether or not other growths were susceptible to this influence; for it is well known that tumors differ among themselves in their reactions to various agencies. A similar experiment was accordingly carried out with the mouse carcinoma 11, a tumor with a growth rate somewhat slower than that of the Ehrlich sarcoma, and the ability to take in 100 per cent of animals.

The details of the experiments may be given briefly as follows: A healthy growing tumor was selected and 0.003 gram inoculated into each of a series of eggs, and also into mice, ac-

cording to the usual technique. At the end of ten days, the eggs were opened under aseptic precautions and the tumor grafts removed. The largest of these were inoculated (0.003 gram) into a new series of eggs and also into mice, and the procedure repeated until the termination of the experiment.

The tumors proliferating in the chick maintained their usual growth characteristics until the fifth generation (fifty days). While the tumors of the fourth generation were as large and as numerous as those of the first, those of the fifth generation were so small that only enough material was obtained for inoculation into the sixth generation of eggs. On opening the eggs of this, the last generation, only a few pinhead nodules were found, too small for inoculation. The experiment was terminated, therefore, from lack of material to continue it, after the tumor had resided sixty-one days in the chick.

The results of the inoculations into mice after the tumors had grown in the chick for varying periods of time, were inconclusive, because after the fourth generation there was not enough tumor to make these implantations. The growths in mice derived from the various generations in the chick showed no constant variation from the controls. Those resulting from the first, second, and third generation were fewer in number and smaller than their controls; but those resulting from the fourth generation were almost as numerous, and of a size equal to the controls. It may be supposed, however, that if mice instead of eggs had been inoculated from the fifth generation, a definite difference between these and control series would have been found. A comparison of the results with the Ehrlich sarcoma and those obtained with tumor 11 brings out considerable difference. The former exhibited impaired growth after one generation and striking impairment after two generations in the chick, while the latter showed no apparent modification after four generations in the chick. The explanation of this is not obvious. It may be due to the fact that the Ehrlich sarcoma is of more rapid growth rate than tumor 11, and is therefore more susceptible to the inhibiting influence.

In a previous report (5) it was pointed out that spleen grafts growing on the allantois of the chick have no influence upon the growth of tumor grafts similarly located. From this finding, and from the fact that foreign tumors grow so well in this medium, it may be assumed that the chick embryo has no active resistance against such tumors until about the eighteenth day, and, furthermore, that active resistance to tumors can not be induced in the chick embryo. If this be true, it is probable that the effect upon a tumor grown for a long time in the chick is produced, not by an active resistance, but because the tumor is unable longer to break down the foreign proteids and convert them to its use. The fact that the tumor of more rapid growth shows this retarding influence first is in favor of this view, for a tumor of this character will need more energy in the same time than one of slower growth. If there is a limit to the energy a tumor can derive from the chick as a foreign soil, which seems to be probable, the tumor of more rapid growth will be the first to manifest exhaustion.

SUMMARY

The growth rate characteristic of tumors in their native species is preserved for one generation in the chick embryo.

During this period there is no evidence of either retardation or stimulation of the growth rate of a tumor in this medium.

Tumors tend to preserve not only their morphology, but their power to recover antecedent characteristics, and they mold the chick tissues as readily as they do those of the animal host.

There is little hope of being able to maintain a tumor of slow growth indefinitely in the chick. Consequently the cultivation of human tumors in the chick embryo for more than a short period of time does not seem likely to be realized.

The organization of tumor grafts in the chick takes place in a manner similar to that in the original species, but the procedure is more rapid.

The chick exerts an unfavourable influence upon tumors growing in it. This is probably due to a lack of suitable nutritive

material rather than to an active immunity. A tumor will grow in this medium only for a limited time, the period depending upon its growth characteristics.

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THE PART PLAYED BY THE HYDROXY-BENZOL RADICAL IN THE ACCELERATION OF THE GROWTH OF CARCINOMATA BY CHOLESTEROL AND BY TETHELIN

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I. INTRODUCTION

In previous communications (1) we have shown that cholesterol, when administered subcutaneously in doses of 40 mgm. at intervals of from two to three days, very decidedly accelerates the growth of the Flexner-Jobling carcinoma in rats. This acceleration occurs whether the administration is adjacent to the tumor or distant from it; and not only is the primary growth affected, but the percentage of metastases is very greatly increased.

Our results have been confirmed in a very striking manner by Sweet, Corson-White, and Saxon (2) who, from a tumor which had never previously yielded metastases, obtained, by the administration of cholesterol by mouth, no less than 104 metastases out of 116 inoculations. Nor was this an isolated result, for employing both normal and restricted diets it was found by these observers that the addition of cholesterol increases the growth of the primary tumor and the incidence of metastases.

Certain comments made by these observers upon their results, as also by Woglom in a recent article (3), have made us realize, however, that our original articles upon this subject must have been deficient in clarity of expression, for our views regarding the mode of action of the cholesterol appear to have

been to some extent, and in important particulars, misunderstood; while Woglom, at all events, has read conclusions into our statements which we never intended to imply.

Thus Sweet, Corson-White, and Saxon, in commenting upon the remarkable effects of administration of cholesterol, make the following statements:

> We are nevertheless unable to agree with Robertson and Burnett that cholesterol is a factor of decisive importance. . . . . A study of Tables III and V shows that animals placed on the Osborne and Mendel diet have developed, in spite of the cholesterol, the same resistance towards tumor takes that has characterised our work with this diet. It would seem, therefore, that the action of cholesterol must depend not upon its action alone, but upon its action when combined with some unknown element of the food.

These observers appear to believe that there is a lack of harmony between their experimental results and the views concerning the relation of cholesterol to tumor growth which we have expressed in our communications. On the contrary, however, we believe that the results obtained and views expressed by Sweet, Corson-White, and Saxon are in entire harmony both with our experimental findings and our interpretation of these findings.

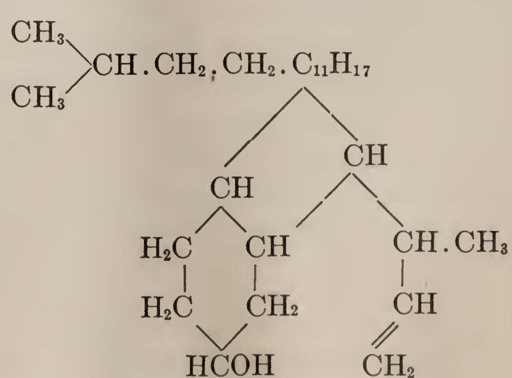
There can be no question but that the action of cholesterol is not attributable to its nutritive value. The nutritive value of the minute quantities of cholesterol employed is a negligible proportion of the total energy-intake of the animals and, moreover, so far as we at present know, cholesterol is not in any large proportion available as a source of energy in the diet. The form of the normal growth-curve of animals (4), as well as the dependence of normal growth upon the presence of minute proportions of certain special factors of negligible calorific value in the diet and upon the normal functioning of the glands of internal secretion, all combine to demonstrate that specific catalysors of growth exist, and we regard and always have regarded cholesterol as constituting one, possibly among many, of these catalysors of growth. Now the Osborne-Mendel diet

employed by Sweet, Corson-White, and Saxon, while supplying a sufficiency of calories and nitrogen, is deficient in lysin, an amino-acid constituent of tissues of which the endogenous metabolism is reducible to zero, but which cannot be synthesized by mammalian tissues. These animals were therefore, in so far as the production of new tissue was concerned, in a condition of starvation, and any new tissue produced, for instance tumor tissue, could only arise by destruction of the tissues of the host. A catalysor cannot accelerate a reaction of which the substrate has already been exhausted, or reinaugurate a reaction in which equilibrium has already been attained. Albeit acids accelerate the hydrolysis of cane sugar, yet when the supply of cane sugar has been exhausted, the further addition of acid will not avail to increase the yield of invert-sugar. We therefore regard the results of Sweet, Corson-White, and Saxon as furnishing substantial support of the view that cholesterol is a catalysor of certain types of growth and particularly of that type which is involved in the growth of carcinomata. Whether we regard cholesterol as a factor of "decisive importance" or not, depends of course upon our definition of what is "decisive." Perhaps, since the raw material or substrate of any chemical reaction is an absolute prerequisite for its occurrence, we might appropriately consider the supply of truly nutritive factors, i.e., calories and the building-stones of tissue, as constituting the only really decisive factors in any type of growth. The underlying idea, both in this remark and in the criticisms of Woglom to which reference has been made, appears to be the mistaken one that we have regarded cholesterol as a cause of tumor growth in the sense that it can initiate tumors. We have, on the contrary, merely expressed the view, which is after all nothing more than a restatement of the facts, that cholesterol is a factor which favors tumor-growth when the conditions precedent to its initiation are present, and we have suggested that the high percentage of cholesterol alleged by Wacker (5) to characterise the subcutaneous fats of aged individuals, may assist materially in determining the increased incidence of carcinoma with advancing age. It must be recollected that the estimation of the

age of incidence of tumors is limited by the possibility of diagnosis. In other words, the necessary conditions precedent to the *initiation* of tumor-growth may be present long before the actual growth of neoplasms renders diagnosis possible. Any condition, therefore, which favours rapid growth in neoplasms once initiated, will play an important part in determining our estimate of the age of incidence.

As a matter of fact we have repeatedly attempted to initiate the growth of neoplasms in normal animals by massive administrations of cholesterol, and we have in every instance failed to obtain any evidence of the development of malignant growths in consequence of such administrations when unaccompanied by the inoculation of tumor-tissue.

The ability of cholesterol to accelerate the growth of carcinomata must undoubtedly depend directly or indirectly upon its chemical structure. We have recently found that another catalysor of growth, namely tethelin, the active principle of the anterior lobe of the pituitary body, is similarly able to cause a very marked acceleration of growth in the Flexner-Jobling carcinoma in rats (6). Now cholesterol and tethelin have this in common: both contain a hydroxy-benzol group. From the investigations of Windaus (7), von Fürth (8) and others, it appears that cholesterol has the formula:



Tethelin has been shown by Robertson (9) to yield inosite, or hexahydroxy-benzol, when split by boiling with barium hydroxid succeeded by sulphuric acid.

The existence of a common radical in these two catalysors of carcinomatous growth necessarily leads to the suspicion that this radical may play an important part in determining their action. It therefore appeared of importance to carry out a series of experiments to determine the effect of modification of this radical in cholesterol upon its ability to accelerate the growth of tumors, and also to determine the effects of a variety of related compounds upon this type of growth. Accordingly the following experiments were undertaken:

II. EXPERIMENTS WITH ACETYL-CHOLESTEROL

Acetyl-cholesterol was prepared from Merck's cholesterol by the method of Raymann (10) and Reinitzer (11) as follows:

Twenty-five grams of cholesterol was boiled with 500 cc. of acetic anhydride for sixteen hours under a reflux condenser. The mixture was then poured into 2 liters of distilled water. The precipitate was washed repeatedly in 2 liter lots of water by suspending it in the water and filtering, until the reaction of the wet precipitate was neutral to litmus. The precipitate was next dried on a water-bath, dissolved in a mixture containing 1 part by volume of alcohol and $1\frac{1}{2}$ parts by volume of ether, filtered, and evaporated until the greater part of the material had crystallized out.

A large yield (25.2 grams) was obtained of acicular white crystals which were slightly yellowish in mass. The melting point was 112°C. (uncorrected). The melting point of acetyl cholesterol is, according to Raymann, 113°C., and according to Reinitzer, 114°C.

Seventy-two rats were inoculated in the axillary region with the same strain of the Flexner-Jobling carcinoma that we have employed in previous investigations. The "takes," determined after twenty-one days, were 86 per cent. Fifty-six of the animals displaying vigorous growths were then divided without selection into two batches of 28 animals each. The one batch was employed as controls, while the others received 40 mgm. of acetyl-cholesterol suspended in $\frac{N}{10}$ sodium oleate solution

every second or third day, the tumors being measured on the dates of administration. The acetyl-cholesterol suspension was administered subcutaneously on the side of the body opposite the tumor. The following were the results obtained:

TABLE 1

DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	14.1	13.9	100.0	100.0
23	15.7	14.9	111.3	107.2
25	17.9	16.9	127.0	121.6
28	18.8	18.4	133.3	132.4
30	19.6	19.5	139.0	140.3
32	20.1	19.6	142.6	141.0
35	22.2	21.4	157.4	154.0

It will be seen that there is no evidence whatever of acceleration of the primary tumor due to the administration of acetyl-cholesterol. Nor was any decisive increase of metastasizing tendency noted, for while 24 of the control animals killed sixty-three days after inoculation yielded only 1 case of metastases in the lung, 23 of the treated animals yielded only 2 such cases.

The replacement of the hydroxyl group by an acetyl group therefore robs cholesterol of its power of accelerating the growth of carcinomata. In interpreting this result, it is of importance to recollect that esters of cholesterol are not hydrolysable by lipase, so that unless some special and as yet unknown mechanism exists whereby compounds of this type may be broken down in the tissues, the hydroxyl group is permanently neutralized by esterification.

It is of especial interest to note in this connection that the action of cholesterol in inhibiting the hemolytic action of saponins is also destroyed by replacing the hydroxyl group (12).

We have noted that acetyl-cholesterol differs very markedly from cholesterol in its lack of emulsifiability in sodium oleate solutions. If 4 grams of cholesterol be triturated with a small volume of hot $\frac{N}{10}$ sodium oleate solution, suspended in 100 cc.

of the hot solution, heated to boiling, and allowed to cool, a very stable milky white emulsion of cholesterol is formed (13). Acetyl-cholesterol, when treated in a similar fashion, immediately separates out from the solution, and the mixture therefore has to be thoroughly stirred up before each administration to the animals.

Acetyl-cholesterol, like cholesterol itself, causes large, granulomatous, subcutaneous thickenings at the point of injection.

III. EXPERIMENTS WITH CHOLESTERYL-CHLORIDE

Cholesteryl-chloride was prepared according to the method of Mauthner and Suida (14) as follows:

Fifty grams of cholesterol was rubbed up with 27 grams of phosphorus pentachloride and allowed to stand over night. On the following morning the solid mass was pulverized, and triturated with water, and after the excess of water had been poured off the mixture was heated for some hours on a water-bath. The mixture had then become pasty, and after cooling on ice it was easily crumbled. The mass was now extracted with a large volume of ether and the resultant solution evaporated at room temperature to a small volume; several volumes of alcohol were now added and the mixture allowed to stand overnight. An abundant crop of crystals was deposited and also some yellow waxy globules which were picked out from the rest by hand and rejected. The crystals were dissolved in ether and recrystallized by evaporation at room temperature. The yield was 27 grams of white acicular crystals with a yellowish tinge in mass.

White rats inoculated with the same strain of Flexner-Jobling carcinoma as that used in our previous experiment were sorted out, the small percentage of immune animals rejected, and the vigorously growing tumors separated without selection into two batches. Twenty-one of the animals were retained as controls, and 20 received every second or third day, on the dates on which the tumors were measured, 40 mgm. of cholesteryl-chloride administered subcutaneously on the side opposite the tumor. The following were the results obtained:

TABLE 2

Cholesteryl chloride

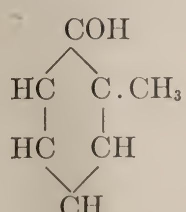
DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	15.5	14.75	100.0	100.0
23	16.2	15.4	104.5	104.4
25	17.7	17.3	114.2	117.3
28	20.0	19.1	129.0	129.5
30	20.4	20.8	131.6	141.0
32	20.8	22.9	134.2	155.3
35	23.5	22.9	151.6	155.3

No evidence of decisive acceleration such as is obtained with cholesterol is afforded by these results. Neither the controls nor the treated animals exhibited any metastases. We may infer that replacement of the hydroxyl by chlorine, no less than its replacement by an acetyl group, robs cholesterol of its power to accelerate the growth of carcinomata. We also noted that cholesteryl chloride, like acetyl cholesterol, does not form stable emulsions when suspended in hot sodium oleate solution.

The importance of the hydroxyl group in determining the accelerative action of cholesterol upon the growth of carcinomata, which is demonstrated by these results, led us to investigate the action of a number of other hydroxy-benzol derivatives.

IV. EXPERIMENTS WITH META CRESOL

Meta cresol:



contains a hydroxyl group which is directly attached to a methylated benzol ring.

Two batches of 25 animals each were chosen without selection from a number with vigorously growing tumors. One lot was retained as controls, while to the individuals comprising the other batch 1 cc. of a 3.5 per cent solution of meta cresol in distilled water was administered on the dates enumerated in the accompanying table. Nearly all the animals showed symptoms of intoxication consequent upon the administration, and two or three of the smaller animals died from this cause. The following were the results obtained:

TABLE 3

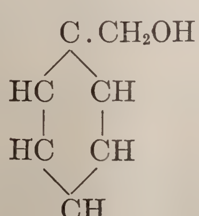
Meta cresol

DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	12.4	13.4	100.0	100.0
23	14.3	13.9	115.3	103.7
25	14.3	15.1	115.3	112.7
27	15.7	17.2	126.6	128.4
30	17.6	17.9	141.9	133.6
34	20.4	21.3	164.5	159.0

No evidence of any acceleration of the growth of the tumors consequent upon the administration of meta cresol is afforded by these results.

V. EXPERIMENTS WITH BENZYL ALCOHOL

In benzyl alcohol:



the hydroxyl group is attached to the benzol ring through the intermediation of a methyl group.

Two batches of 25 animals each were employed, chosen without selection from among a number with vigorously growing tumors, one being retained as controls and the other receiving 1 cc. of a 4 per cent (saturated) solution of benzyl alcohol in distilled water every second or third day, administered subcutaneously on the side of the animal remote from the tumor. The following were the results obtained:

TABLE 4

Benzyl alcohol

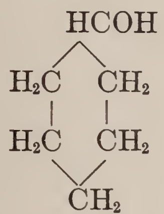
DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	14.0	13.8	100.0	100.0
23	14.1	15.2	100.7	110.1
25	15.6	15.8	111.4	114.4
28	16.5	17.0	117.9	123.2
30	17.6	18.2	125.7	131.9
32	18.6	18.9	132.9	137.0
35	19.5	20.3	139.3	147.1

While a tendency is displayed in these experiments for the growth of tumors in animals treated with benzyl alcohol to maintain a slight advance over that of the tumors in the controls, we cannot regard this as constituting evidence of a decisive acceleration in any degree comparable with that attainable by the administration of cholesterol. We regard these results as failing to establish any accelerative action of benzyl alcohol upon the growth of carcinoma. Neither the controls nor the treated animals yielded any metastases after fifty days.

VI. EXPERIMENTS WITH HEXAHYDROPHENOL

Benzyl alcohol does not afford a true analogy to the structure of the hydroxy-benzol nucleus in cholesterol, because in benzyl alcohol the hydroxyl is attached to the benzol ring through a methyl group, and, moreover, in cholesterol the benzol group is reduced, i.e., contains hydrogens attached to the ring which

are absent both in benzyl alcohol and in meta cresol. In seeking for a substance more analogous to cholesterol we consulted our colleague Dr. H. C. Biddle, who drew our attention to hexahydrophenol, with a sufficient quantity of which he was also so kind as to furnish us. This substance, which has the formula



is a clear liquid, readily soluble in water.

Two batches of 20 animals each were chosen without selection from a number with vigorously growing tumors, one batch serving as controls and the other receiving subcutaneously 1 cc. of a 4 per cent aqueous solution of hexahydrophenol every second or third day on the side of the animal remote from the tumor. The following were the results obtained:

TABLE 5

Hexahydrophenol

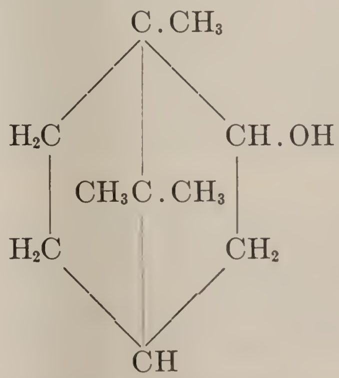
DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	15.5	16.1	100.0	100.0
23	16.2	16.6	104.5	103.1
25	17.7	19.6	114.2	121.7
28	20.0	21.6	129.0	134.2
30	20.4	23.2	131.6	144.1
32	20.8	24.5	134.2	152.2
35	23.5	25.1	151.6	155.9

Again a slight tendency is displayed for superior growth in the treated animals. The effect is slight and irregular, however, and almost disappears in the last measurement. It is most probably to be accounted for by the initial inequality of the two batches of tumors selected at random. We regard this

experiment as failing to establish any decisive acceleration due to hexahydrophenol. Neither the treated nor the control animals yielded any metastases sixty-six days after inoculation.

VII. EXPERIMENTS WITH BORNEOL

Benzyl alcohol, meta cresol, and hexahydrophenol are all highly soluble substances, while cholesterol is insoluble in water. We therefore sought a substance analogous to cholesterol in the possession of a reduced hydroxybenzol radical and also insoluble in water, arguing that the ready solubility of the substances previously employed might so facilitate elimination that the quantity present in the tissues at any moment would be insufficient to affect tumor growth in any notable manner. We accordingly employed borneol:



with which substance Dr. H. C. Biddle again very kindly supplied us.

Two groups of animals, the one consisting of 25 controls and the other of 20 animals which were subsequently treated, were chosen at random from among a number with vigorously growing tumors, and treated as in previous experiments. The borneol was administered in the form of a 4 per cent suspension in $\frac{N}{10}$ sodium oleate solution, the dosage being 1 cc. of the suspension every second or third day, administered subcutaneously on the side remote from the tumor. The following were the results obtained:

TABLE 6

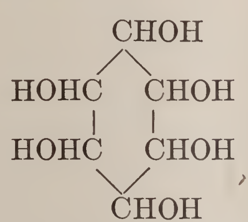
Borneol

DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	12.4	12.5	100.0	100.0
23	14.3	13.6	115.3	108.8
25	14.3	14.6	115.3	116.8
27	15.7	16.1	126.6	128.8
30	17.6	17.2	141.9	137.6
34	20.4	20.5	164.5	164.0

The results are decisively negative. Shortly after the conclusion of this experiment we lost all our animals through an epidemic, and no record of metastases was therefore obtained.

VIII. EXPERIMENTS WITH INOSITE

This substance, hexahydroxy-benzol,



is of exceptional interest in this connection because it is a product of the hydrolytic cleavage of tethelin, which we have shown to possess a very marked ability to accelerate the growth of carcinomata. Ten grams of this substance, prepared and purified by himself, were very generously supplied to us by Dr. R. J. Anderson, to whom we wish to express our sense of indebtedness.

In these experiments we were forced, owing to the death of our animals, to employ a new strain of the Flexner-Jobling carcinoma, which was very kindly supplied to us by Dr. P. K. Gilman. In its first inoculation into our animals, this strain behaved very differently from the strain to which we have become accus-

tomed. The percentage of takes was as high as in our own strain, i.e., about 90 per cent; but growth during the first three weeks was unusually rapid, so that we commenced administration of the inosite when the tumors were far more advanced in development than in our experiments reported above. Two batches of 22 animals each were chosen at random from among a number with these vigorously growing tumors. One batch was retained as controls, while the individuals comprising the other received 1 cc. of a 4 per cent solution of inosite in water, on the side remote from the tumors, on the dates enumerated in the table. The following were the results obtained:

TABLE 7

Inosite

DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	20.6	22.9	100	100
23	22.9	23.9	111	104
25	25.0	28.6	121	125
28	27.7	30.9	134	135
30	30.5	33.2	148	145
35	34.8	36.9	169	161

We were unable to regard these results as conclusive, first because of the unusually rapid growth of the tumors in untreated animals, indicating that the velocity of growth, even in the absence of specially administered catalysors, was already at a maximum; and also, because of the accidental disproportion between the initial dimensions of the tumors in the two groups chosen at random for the purpose of comparison. We therefore inoculated a fresh batch of animals from the controls of this experiment and obtained a series of tumors corresponding much more closely with our previous experience of the mode of growth of the Flexner-Jobling carcinoma in rats. From among these animals we selected two batches of twelve animals each, modifying our original random selection so as to render the initial average diameter of tumors in both batches the same. One

batch being retained as controls, the other was treated in the manner outlined above. The following were the results obtained:

TABLE 8

Inosite

DAYS AFTER INOCULATION	AVERAGE DIAMETER OF TUMORS IN MILLIMETERS		AVERAGE DIAMETER OF TUMORS IN PERCENTAGES	
	Controls	Treated	Controls	Treated
21	16.8	16.7	100.0	100.0
23	19.3	18.3	115.0	109.7
26	22.4	21.0	133.4	125.7
28	24.1	21.7	142.9	130.0
31	26.1	24.2	155.4	144.9

The results of this experiment are entirely confirmatory of those of the first experiment, and show that inosite administered in the doses specified does not to any appreciable extent accelerate the growth of carcinoma.

IX. SUMMARY OF THE RESULTS

From the results enumerated above we may infer: (1) That the accelerative action of cholesterol upon the growth of carcinoma is dependent upon its hydroxyl radical. (2) That the hydroxy-benzol radical in a variety of other compounds does not produce the characteristic acceleration of the growth of carcinoma that cholesterol does.

Two alternative interpretations of these results offer themselves, between which, at the present moment, we do not feel able definitely to decide. The one is, that the hydroxy-benzol group in cholesterol and tethelin acts as an anchoring group, enabling cholesterol and tethelin to attach themselves to the tumor tissue, while other portions of these molecules are responsible for the stimulation of growth. Against this supposition, in so far as it affects cholesterol, may be urged the fact, ascertained by Bennett (15), that the administration of cholesterol to animals possessing tumors does not lead to any notable increase of the cholesterol content of the tumor-tissue. The

alternative explanation is, that the analogous structures of cholesterol and tethelin, in so far as their common possession of a hydroxy-benzol group is concerned, bear no necessary relation to their analogous actions upon the growth of carcinoma, and that the effect of deprival of the hydroxyl group in preventing the accelerative action of cholesterol upon the growth of carcinomata is attributable to the non-emulsifiable character of derivatives of cholesterol which do not contain a free hydroxyl. This lack of emulsifiability would imply difficulty of distribution throughout the tissue fluids, and this mode of interpreting our results would involve the supposition that the accelerative action of cholesterol is dependent, not upon its concentration within the tumor tissue itself, but in the fluids bathing the exterior and growing parts of the tumor tissue. That the administration of an excess of cholesterol to the animals does lead to a decided increase in the cholesterol-content of the blood, has been recently shown by Luden (16).

CONCLUSION

1. The accelerative action of cholesterol upon the growth of carcinoma is dependent upon the hydroxyl radical.

2. Other hydroxy-benzol derivatives, namely meta cresol, benzyl alcohol, hexahydrophenol, borneol, and inosite, do not cause any decisive acceleration of tumor growth.

3. We infer that the accelerative actions of cholesterol and tethelin are not due to their possession of a hydroxy benzol group, but that the accelerative action of cholesterol is in some way rendered possible by its possession of a hydroxyl group. The hydroxyl group may act as an anchoring group, fixing the cholesterol to the tissue, or it may merely facilitate the distribution of cholesterol throughout the tissue-fluids by rendering the cholesterol emulsifiable.

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CASES OF TYPICAL AND ATYPICAL LYMPHOSARCOMA

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The classical descriptions of Kundrat (1) and Paltauf (2) differentiated lymphosarcoma from the group which in the older literature had all been called malignant lymphomas. The conception of Sternberg, who reviewed the subject in 1903 and added his own observations, is briefly as follows (3): Lymphosarcoma is a tumor formation starting in a group of lymph nodes and spreading thence to neighboring nodes or follicles. It spreads from region to region without ever exhibiting such general lymphoid involvement as leukemia or pseudoleukemia. Sooner or later it invades the capsule and extends into the surrounding tissue. Metastases differ from those of ordinary neoplasms in that the intervening lymphoid tissues are affected. True metastases, which can be explained only through transfer by way of the blood stream, are rare, and usually isolated. Blood-vessels are seldom invaded by lymphosarcoma, being usually only surrounded and narrowed. The commonest sites of origin are the lymph nodes of the neck, mediastinum, mesenteric and retroperitoneal regions; less frequently the inguinal and axillary nodes. The affected groups form nodular, uneven masses, well limited in the beginning, but later diffusely permeating the surroundings; they are mostly hard, grayish-white, and show a homogeneous cut surface. In general, when a hollow organ is invaded, the growth tends to form a sleeve-like mass about it, usually, however, causing no obstruction, but, on the contrary, tending to widen the lumen. The spleen is rarely attacked and the bone-marrow likewise. Histologically, the tumor is characterized by an irregular reticular framework with lymphoid

cells in the meshes; the architecture of the node is lost; follicles and medulla are no longer differentiated, and the capsule and surrounding tissue are diffusely infiltrated with tumor cells so that the separate lymph nodes can neither be distinguished from one another nor from the surrounding tissue. Often the tumors show an alveolar structure. The cells resemble lymphocytes but are larger, have a more lightly staining nucleus, and a scanty, often almost invisible, non-granular cytoplasm. There is no definite alteration of the blood picture.

The eight cases described by Dr. MacCallum (4) fall quite clearly into this group. Of his cases, none of the three which belonged to the intrathoracic type showed metastases in distant organs. The dissemination of the tumor masses conformed strictly to Kundrat's idea of regional distribution. Indeed, in one of these cases, the tumor had penetrated the heart wall and hung in polypoid masses within the heart without metastasizing by the blood stream. Of the five cases in which the intestinal lesion forms the constant feature, two showed single metastatic nodules in the liver and another had metastases in the liver, thymus, bone-marrow, and kidneys; but these, from the description, seem to have been more like infiltrations, using the framework of the organ as their support, rather than metastatic nodules. The structure of the tumors and the characteristics of the cells, as well as the pathological anatomy in Dr. MacCallum's cases, agree quite closely with Sternberg's description of the Kundrat-Paltauf lymphosarcoma.

The descriptions by Kaufmann (5) and Naegeli (6) agree with those mentioned. The former, however, speaks of two types of lymphosarcoma: the regional and the generalized. The latter he regards as rare, but reports a case of a man, twenty-five years of age, in which a primary lymphosarcoma of the small intestine was associated with metastases in the skin, pericardium, pleura, lung, bone-marrow, and kidneys. Naegeli, too, observes that in the late stages one may find widely distributed nodules.

It is clear, then, that the occasional occurrence of a widespread dissemination of metastases has been well recognized, but

in general these colonies have been described as diffuse infiltrations rather than as distinct circumscribed nodules. The spleen has been considered as almost immune to the tumor.

The four cases included in this report have been taken from the autopsy records of the past five years at the Presbyterian. It would take too long to attempt to give a complete account of each case, but the summaries include the essential features.

Case I. A man of fifty-eight, who six months before admission to the Presbyterian Hospital, in September, 1912, noticed a large lymph node in the left groin. Three weeks later the superficial lymph nodes all over the body were enlarged. The legs, and then the abdomen and scrotum, became swollen. Physical examination showed great enlargement of all the superficial lymph nodes, fluid in the abdomen, enlargement of the liver, and oedema of the external genitals and lower extremities.

Blood count.

Red blood cells	3,600,000
Haemoglobin	80 per cent
White blood cells	9,600
Polymorphonuclears	79
Lymphocytes	16
Large mononuclears	5
Eosinophiles	0

Three weeks later

White blood cells	12,000
Polymorphonuclears	80 per cent
Small lymphocytes	12 per cent
Large lymphocytes	6 per cent
Eosinophiles	3 per cent

All the lymphatics steadily enlarged and fluid accumulated in the chest. The spleen enlarged so that the edge was felt 6 cm. below the costal border; the edge of the liver was 7.5 cm. below the costal border. A large, firm mass was felt in the pelvis on rectal examination. There is no note in the record of an examination for Bence-Jones protein.

Autopsy. There was a great enlargement of all the superficial lymph nodes. Surrounding the rectum, and nearly filling the pelvis, to the walls of which it was adherent, there was a tumor which extended upward and involved the retroperitoneal lymph nodes, surrounding each ureter, the aorta, and the inferior vena cava. Extend-

ing from the mass about the inferior cava, the tumor had infiltrated the right kidney, diffusing itself gradually out to the cortex. The pericardium was studded with irregular nodules and was adherent to both lungs. The pleural surface of each lung was marked with small nodules and tumor tissue was also found passing into the lung about the bronchi. The mediastinal and bronchial nodes were much enlarged. The liver contained no tumor nodules. The spleen measured 18 by 10 by 7 cm. It showed some small anaemic infarcts and on the cut surface innumerable small white foci appearing like enlarged malpighian corpuscles. There was no tumor in the pancreas nor in the left kidney. The oesophagus had a great many very small nodules on the mucous membrane. The stomach and intestine exhibited no evidence of tumor, nor was the lymphoid tissue unusually prominent. The bone-marrow of the femur contained some very small nodules scattered through it.

Microscopical examination. Microscopically the tumor has the same appearance wherever found. The architecture of the lymphoid tissue is entirely lost, the tissue being overwhelmed by tumor cells. The stroma is scanty; the tissue is only moderately vascular. The cells show considerable uniformity in size and shape; they are a little larger than lymphocytes, stain less deeply, and have little or no visible cytoplasm. No tendency toward an alveolar structure is evident. The capsule of the lymph nodes has been invaded, and dense accumulations of cells are found scattered diffusely through the surrounding tissue. In the spleen, the tumor cells have formed follicle-like masses two or three times the usual size of malpighian corpuscles.

Case II. The patient was a man of fifty-five admitted to The Presbyterian Hospital January 4, 1916. He had had a chancre and secondary lesions twenty-three years ago. For seven months before admission to the hospital he had had intermittent sharp darting pains in the back, about the shoulders, and in the groins. Various forms of treatment gave no relief. Physical examination showed a stout plethoric man with slight cyanosis, a little exophthalmos, nystagmus and inequality of the pupils. Heart a little enlarged to the left, systolic murmur at the apex, and occasional extra systoles. There was also a right inguinal hernia. Superficial lymph nodes were not enlarged. Neither liver nor spleen was palpable.

Blood count.

	JANUARY 3	JANUARY 7	JANUARY 8	JANUARY 10	FEBRUARY 1	FEBRUARY 10
White blood cells.......	18,000	25,000	16,800	20,600	14,400	18,200
Polymorphonuclears....	70	73	78	73	70	73
Small lymphocytes.....	30	22	17	21	23	11
Large lymphocytes.....	0		2	5	2	
Eosinophiles...........	0	2	0	1	0	2
Transitionals...........	0	3	2	0		
Haemoglobin...........	90 per cent				5	14

Wassermann. Alcoholic antigen, negative; cholesterin antigen, negative.

Spinal fluid. Normal.

Phthalein. 28 per cent in two hours.

McLean Ambard index. 95.5.

Examination of stool. No blood, pus, ova, or parasites.

Gonococcus complement fixation. Negative.

Pain in various parts of the body persisted, he became paralyzed below the waist, lost control of bladder and rectum, and developed oedema of the legs. By rectal examination a mass was felt above the prostate and hard irregular masses were noted in the left side of the abdomen.

Urine. Specific gravity, 1020 to 1037. Acid. Albumin—very faint trace. Glucose, none. Microscopic, hyaline and granular casts.

Temperature and pulse. Normal till just before death.

Blood pressure. 124/74.

Autopsy. The lymph nodes along the aorta and in the mesentery were greatly enlarged. The grayish tissue by which they were replaced had extended through their capsule and invaded the fat about them, forming a large mass almost completely surrounding the aorta and vena cava from the diaphragm to the pelvis. There were nodules also in the fat about both kidneys. The bronchial lymph nodes were enlarged and composed of tumor tissue. A single node in the lower part of the cervical chain, measuring 1 cm. in diameter, was composed of tumor. The pleural surface of each lung contained nodules, and numerous whitish tumors projected from the liver, the largest measuring 2 cm. in diameter. The spleen weighed 85 grams and seemed to be normal. The dura of the spinal cord, from the 8th dorsal vertebra upward, was infiltrated by a sheet of tumor measuring 1 to 3 mm. in thickness. It had surrounded the roots of the nerves as they passed

out, but did not appear to have exerted pressure on the cord itself, nor were the vertebrae invaded. The other organs showed nothing of interest.

Microscopical examination. Here again the invasive quality and loss of the lymphoid tissue are evident in the sections. In vascularity and in the amount of connective tissue framework, this case is quite similar to the first, but in both the primary tumor and the metastases there is a more marked tendency toward an alveolar arrangement.

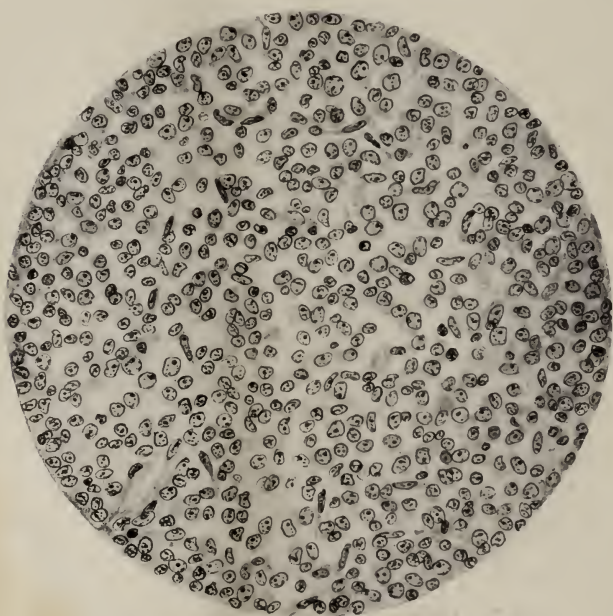

FIG. 1. CASE II

Drawing showing character of tumor cells in the metastatic nodules in pleura and liver. The cells are slightly larger than lymphocytes, are more irregular in shape, and have vesicular nuclei.

Except for their slightly greater size, the cells of the primary growth in the abdominal lymph nodes resemble normal lymphocytes quite closely; they are 8 to 10 micra in diameter, the nucleus is round, deeply stained, and surrounded by only a narrow rim of cytoplasm. In the liver, spinal meninges, and pleural metastases, the cells are larger, more irregular in shape, and have more vesicular nuclei. In the bone marrow there are small discrete foci of tumor cells.

These two cases, it seems, may be classed as belonging to the Kundrat-Paltauf group. In the first, the primary tumor was apparently about the rectum; from here it had extended to practically all the lymphoid tissue in the body and had extensively infiltrated the surrounding tissues. The foci in the spleen and marrow are unusual features but the occasional occurrence of such metastases has been recognized. The primary growth in the second case was evidently in the lymph nodes about the aorta. The invasion of the spinal meninges with the clinical picture dominated by spinal cord symptoms, and the discrete nodules in the liver, were the atypical features here.

Microscopically, both of these cases agree well with the descriptions of Drs. MacCallum, Sternberg, Paltauf, and Kundrat.

The two following cases are more atypical, and hence more difficult to classify.

Case III. The patient was a Russian woman of forty-four, who entered the Presbyterian Hospital August 1, 1916. There was nothing important in the family history or past history.

Seven months before admission to the hospital she noticed enlarged nodes in each inguinal region. Three months later, those in the left axilla became enlarged and subsequently all the other superficial lymph nodes. On physical examination there was found general enlargement of all the superficial nodes, without any tenderness; signs of fluid in the left chest; an enlarged liver, the anterior margin of which extended 8 cm. below the costal border; in the left upper quadrant of the abdomen a very large mass with a notched border taken to be the spleen, and nodular masses in the left lower quadrant also.

Blood count.

Red blood cells	3,240,000
Haemoglobin	70 per cent
White blood cells	5,300
Polymorphonuclears	85 per cent
Lymphocytes	13
Eosinophiles	2

A node was excised from the left axilla and from it an emulsion was made for guinea-pig inoculation. No trace of tuberculosis could be

found in the guinea-pig, however, when it came to autopsy. Examination of the urine for Bence-Jones protein was negative.

Autopsy. At autopsy there were found projecting nodules in the inguinal, axillary, and cervical regions. The lymph nodes about the iliac vessels and the aorta were greatly enlarged, and composed of firm grayish tissue, the largest measuring 6 or 7 cm. in diameter. The capsule of many of the nodes had been invaded, so that in places several were fused together into a single large nodular mass. These masses closely surrounded the aorta, and the vena cava was also embedded in tumor, to which its wall was in places densely adherent. The bronchial and mediastinal nodes were enlarged in the same way and fused into one mass. The psoas muscle on each side, and the lumbar vertebrae, were invaded by direct extension of the tumor from the retroperitoneal nodes.

Lungs. Dense coats of gray tumor tissue were found following the bronchi and blood-vessels into the substance of the lung, and also some button-like nodules on the pleura.

Liver. Weight 1450 grams. It contained numerous projecting nodules of a rather grayish-yellow, translucent appearance; in the region of the cystic duct there was a single large nodule.

Spleen. Weight 1820 grams. It was largely made up of clusters of firm, grayish, more or less discrete nodules of tumor. It showed also large areas of infarction.

Intestines. Normal. No enlargement of the lymphoid structures.

Bladder. There were distinct tumors in the muscular coat.

Uterus, vagina, ovaries, kidneys, adrenals, and aorta. Showed nothing noteworthy.

Bone marrow. The marrow of the lumbar vertebrae was fatty and yellow. In the marrow of the crest of the ileum, a single nodule was found.

Heart, stomach, rectum. Normal.

Microscopical examination. The structure of the tissue and the appearance of the cells is much the same in all the tumor masses. The architecture of the lymph nodes has been entirely lost; there are few blood-vessels and very little stroma, that present being mostly in the form of filaments dividing the tumor cells more or less into groups. The growth has invaded the capsule of the lymph nodes to some extent, but the separation, by the capsule, of the tumor cells within the node from the surrounding tissue, is still distinct. The cells show great variation in size, but average about 12 to 14 micra, though

some are fully three times the size of a lymphocyte; these are often angular and irregular in shape. The well preserved cells have an oval, slightly irregular, or round vesicular nucleus with a sharply marked nucleolus. The cytoplasm is wider than in a lymphocyte and stains a grayish-blue color. Mitotic figures in every stage are abundant. An occasional multinuclear element much larger than the predominating type can also be found after careful searching.

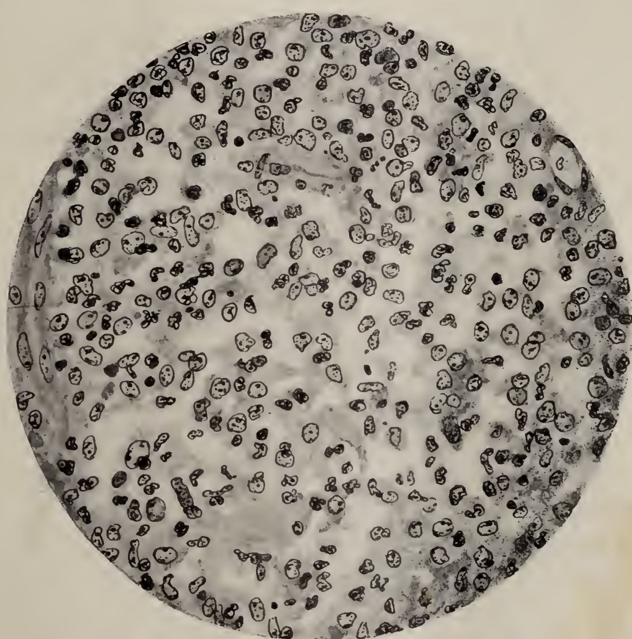

Fig. 2. Case III

Note the great variation in the size and shape of cells, the presence of fragmented nuclei, the poor vascularization, and the lack of stroma.

Case IV. The patient was an Italian of forty-two, admitted to the Presbyterian Hospital in February, 1914, complaining of swelling of the right leg of about eight months' duration. Physical examination showed a firm mass the size of an egg in the right groin, nodular masses in the right lower quadrant of the abdomen, an enlarged spleen extending 5 cm. below the costal border, no enlargement of the liver, and enlarged nodes in the cervical and axillary groups.

Wassermann. Positive +++.
Spinal fluid. Negative.
Blood count.

Red blood cells	5,000,000
Haemoglobin	85 per cent
White blood cells	6,100 to 14,000
Polymorphonuclears	68 to 78 per cent
Small lymphocytes	18 to 26 per cent
Large lymphocytes	2 to 8 per cent
Large mononuclears	1 to 6 per cent
Eosinophiles	1 to 4 per cent
Basophiles	0 to 1 per cent

Urine. A faint trace of albumin and a few hyaline and granular casts.

Blood pressure, pulse, and temperature. Normal.

The superficial lymph nodes steadily enlarged, and became adherent to one another and to the surrounding tissues; great oedema developed in both legs and in the scrotum; the spleen and masses in the abdomen steadily increased in size. The liver was not palpable. A bloody effusion developed in the left chest. Anti-syphilitic treatment had no effect, either upon his general condition or upon the enlarged lymph nodes. Rectal examination disclosed a large mass nearly filling the pelvis. The urine showed no Bence-Jones protein.

Autopsy. In the cervical, axillary, and inguinal regions there were large masses of nodes matted together, none of which, however, was adherent to the skin. The mesenteric and retroperitoneal nodes were greatly enlarged, the largest masses being found just above Poupart's ligament on the right side. In the mediastinum and about the bronchi, the lymph nodes were distinctly enlarged, but less so than in the retroperitoneal chain. The enlarged nodes were generally well encapsulated, although adherent to one another. Nowhere was there a diffuse infiltration of the surrounding tissues. The pleura of the left lung contained large flattened tumor masses; the pleura of the right lung had similar flattened masses but much less extensive. The vessels and bronchi entering the lung were surrounded by coats of whitish tumor, but there were no other nodules in the substance of the lungs. The spleen weighed 2250 grams, the enormous increase in size being due to a great mass of nodules of the same pale gray, firm tumor tissue. A few of the nodules had a yellowish tint and were softer than the others; their average size was about 2 cm. Small masses were also found on

the diaphragm. Heart, aorta, liver, gall bladder, pancreas, adrenals, bladder, and prostate showed nothing noteworthy. The intestines were normal. There was no enlargement of the intestinal lymphoid tissue.

Microscopical examination. The structure of the tumor and the character of the predominating cells are here similar to those in case III, though the nuclei stain somewhat more deeply. In some places, an alveolar arrangement is very definite. The large cells which, in

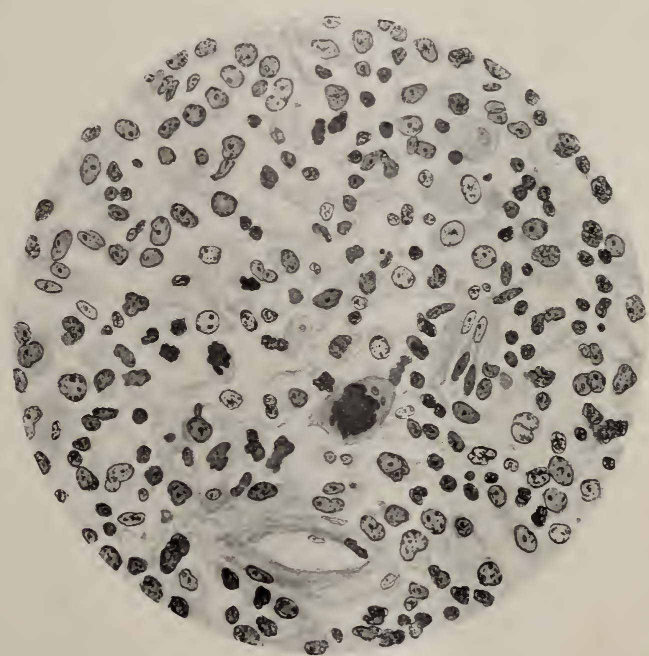

Fig. 3. Case IV

The cells are very large and vary greatly in shape and size. Extremely large cells with irregularly shaped, deep-staining nuclei are common.

case III, were very scarce, are in this case numerous, almost every low power field having four or five. Some of these have several nuclei closely crowded together, others a single, large, convoluted nucleus. The largest of these elements measure 40 to 50 micra in diameter and have a nucleus in most cases staining very darkly and occupying two-thirds to three-fourths of the cell. The non-granular cytoplasm stains a grayish-pink color and is sharply outlined. These cells resemble

somewhat the megalokaryocytes of bone-marrow, although the nucleus occupies relatively more of the cell and is richer in chromatin. The bone-marrow sections show focal accumulations of cells quite the same as those found in the lymph nodes.

The similarity in these two cases (III and IV), is very striking in many particulars. Clinically, the following points of similarity should be noted:—One patient was forty-two, the other forty-four; in one the disease ran its course in nine months, in the other in fourteen months; in both the first lymphatic involvement noticed was in the groin; in both a marked enlargement of all the superficial lymph nodes followed within a few months; both showed enlargement of the liver and great enlargement of the spleen, as well as nodular masses in the lower abdomen; in neither was there a leukemic blood picture.

In their pathological anatomy the two cases are likewise very similar: the general lymphatic enlargement, the tendency of the enlarged nodes to become fused together into large masses without, however, diffusely invading their surroundings, as was the condition in the first two cases; the great enlargement of the spleen from the presence of discrete tumor nodules closely crowded together, the involvement of bronchi, pulmonary vessels, and pleura in a characteristic manner, the absence of any change in the lymphoid tissue of the intestines, and finally, the presence of discrete foci of tumor cells in the bone marrow without the presence of Bence-Jones protein in the urine. All these features were present in both cases. One of them did, however, show discrete nodular metastases in the liver and the urinary bladder, while the other did not.

The resemblance between the two is further borne out by the histological picture. The structure of the tumor tissue, and the size, shape, and staining affinities of the predominating cells are much the same in each. Case IV has, however, many more of the very large cells and these, moreover, are larger and have more darkly staining nuclei than the large cells in case III.

When we try to place these two cases in any of the recognized groups of primary enlargement of the lymphoid tissues,

difficulties are encountered at once. From the Kundrat lymphosarcoma they are distinguished by the following characteristics:

1. The early involvement of the lymph nodes throughout the body, in a manner which does not suggest a regional extension.

2. The formation, in great numbers, of discrete nodular metastases in the liver (case III) and spleen (both cases).

3. The much less marked tendency to grow out into the surrounding tissues, but rather to form large masses of nodes, adherent to one another.

4. The very different histological picture:—the greater average size of the cells and the variation in their size and shape, the more vesicular character of the nuclei, and the presence of very large cells which in one case have an appearance suggesting megalokaryocytes.

From pseudoleukemia or aleucocythaemic lymphatic leukemia these cases are readily differentiated by the type of splenic enlargement, the nodular metastases, and the different histological picture, these cases having cells bearing no resemblance to the lymphocyte.

From the leucosarcoma of Sternberg, assuming that there may be an aleukemic stage or form of this condition, the cases I have described may be differentiated:

1. By the fact that in leucosarcoma the splenic enlargement is due to a diffuse infiltration of the whole spleen by the abnormal cells, and not to the presence of clusters of discrete nodules.

2. The liver is affected in leucosarcoma in the same way as in leukemia, that is, by infiltrations.

3. By the absence in leucosarcoma of the very large cells found in the two cases I have described.

It is hardly necessary to point out that the histological picture alone of Hodgkin's disease is sufficiently characteristic to make it unnecessary to indicate other points of differentiation.

SUMMARY

In conclusion, then, the four cases included in this preliminary report fall into two groups. The first two have enough in

common with the Kundrat-Paltauf lymphosarcoma to be classed as such. The other two cases differ so essentially from lymphosarcoma, pseudoleukemia, and leucosarcoma that to place them in any of these groups seems unjustifiable.

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RESEARCHES ON THE CANCEROUS DISEASES IN NORWAY

AN ABSTRACT [1]

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INTRODUCTION

The Kingdom of Norway occupies the northern and western part of the Scandinavian Peninsula, with a coastline of 1700 miles fronting the Skagerack, the North Sea, and the Atlantic and the Arctic Oceans.

The total area is 124,495 square miles (thus slightly exceeding that of Great Britain and Ireland). The configuration of the country is very extended, making the distance from its southern point, Cape Lindesnes at 58° N.L., to the North Cape at 71° N.L., about 13 degrees of latitude, or 1000 miles or more as the crow flies.

The country is mountainous throughout its whole extent; the greatest elevations are to be found mainly near the western coast, which is protected by innumerable islands and indented by deep, ramified fjords that reach far into the mountainous inland. This is also divided by mountain chains into a great number of valleys, in the southern part of the country mostly converging and opening towards the south-eastern low-lands, in the vicinity of Christiania, the capital.

Only about 4 per cent of the soil is cultivated, 7 per cent being pasturage, 21 per cent forests, and 69 per cent naked mountains, lakes, glaciers, etc.

[1] Undersoekelser over Kræftsygdommene i Norge (Videnskapsselskapets Skrifter. I. Mat-Naturv. Klasse 1916. No. 7), Kristiania.

The population amounts to 2,400,000 inhabitants, irregularly and with greatly varying density scattered over the vast area. Of this population, 71.1 per cent live in the country, and only 28.9 per cent in towns, Norway thus showing a very low percentage of urban population.

Ethnographically, the Norwegian people is very homogeneous; it belongs nearly exclusively to the northern (Scandinavian) branch of the Indo-germanic race. However, chiefly in the far north, there live about 10,000 Finlanders and 20,000 Lapps, both belonging to the Ugrian race.

The Norwegians are generally fair-haired and blue-eyed; the shape of the skull is dolicho- or mesocephalic, and the stature rather tall, Norwegian recruits (of 23 years) averaging a little more than 171 cm. in height. Thus they are perhaps the tallest men in Europe.

On the southwestern coast there is a distinct strain of a brachycephalic fair-haired and tall population.

The average of longevity is very high, the average length of life being 54.8 years for men, 57.7 for women, next to Denmark the highest in Europe. This is, perhaps, mostly due to the low infant mortality.[2]

During the period included in the following researches, Norway has been divided into 158 districts for its medical administration.

The material on which these researches are based is: (1) The official mortality reports for the years 1902–1911, and (2) the material collected by the Norwegian Committee for Cancer Research, 1908–1912.

I. MORTALITY STATISTICS, 1902–1911

1. The increase in the mortality from cancer

The official medical reports of the last half century show a continuous rise in the number of deaths from malignant tumors, from 115 deaths in 1854 to 2182 in 1904, i.e., a proportion of 1 to 18.9.

[2] The average length of life in the United States is 48.3 years for men, 51.9 for women.

But this appalling increase is, of course, only apparent. During the same 50 years the population has grown in the proportion of 1 to 1.6, and the knowledge of the causes of deaths in the proportion of 1 to 7.2 (from 11.9 per cent to 86.3 per cent of all cases).

YEAR	POPULATION MILLIONS	REPORTED DEATHS FROM CANCER	PERCENTAGE OF KNOWN CAUSES OF DEATH	NUMBER OF DOCTORS IN NORWAY
1854	1.447	115	11.9	315
1864	1.658	296	38.4	354
1874	1.774	568	42.9	463
1884	1.922	1006	52.7	610
1894	2.030	1494	68.3	848
1904	2.274	2182	86.3	1138
Increase.......	1:1.6	1:18.9	1:7.2	1:3.6

The real increase in the mortality due to malignant tumors during these 50 years, 1854–1905, *will consequently not exceed the ratio of 1 to 1.66.* And even this figure may probably be somewhat reduced, considering that a constantly increasing number of deaths has been recognized as due to malignant tumors. Still it can not be denied that the figures given tend to show a certain increase in the number of deaths in Norway referable to cancerous diseases, from the middle of the last century up to the present time.

2. Present mortality

During the years 1902–1911, the total mortality from all malignant tumors (carcinoma and sarcoma) in Norway amounted to 22,111 cases, varying slightly from year to year. (In 1914, the cancer mortality was reported to be 2484 cases).

This makes an average annual mortality of 9.5 to 10,000 living, about 7 per cent of the total mortality from all causes.

But during the period in question, the percentage of known causes of death was 87.4, 12.6 per cent of all deaths not being established by the health officers. The above reported number of deaths by malignant tumors may consequently be augmented by 12.6 per cent, in order that the exact figure may be arrived at. If this be conceded, *the mortality from malignant*

tumors in Norway during the years 1902–1911 may be estimated at 10.7 per 10,000, the "*cancer figure.*"

The cancer mortality—cancer figure—calculated in this way varies not inconsiderably in the twenty different counties (*amts*) through the country, this variation ranging from 8.1, in Finmarken (north) to 13.8 in Jarlsberg and Larvik (south), this latter having a very much denser population. As a rule, the counties are of considerable extent, varying greatly within their own boundaries as to soil and living conditions, and consequently, also, as to the conditions favorable to the development of disease. A truer idea can be derived by examining the 158 medical districts, each of them geographically and ethnographically more homogeneous and well-defined.

The cancer mortality in these districts varies considerably more than in the counties, the cancer figures in the districts ranging from 23.2 to 1.8 per 10,000. It must be remembered, however, that the percentage of unknown causes of death varies highly in the different districts, ranging from 0 per cent to 50 per cent, and reaching in one district even as high as 65.2 per cent; this may in some cases make the results obtained less reliable.

The results of these detailed investigations, as shown by the accompanying map, prove that the regions about the Trondhjemsfjord (from 63° to 65° north latitude) represent the greatest continuous cancer-area in Norway.

Among the highly cancerous districts must also be mentioned the well populated districts to the east and south of Lake Mjoesen, as well as the whole of the densely populated county of Jarlsberg and Larvik.

Least affected by malignant tumors are the northernmost counties of the country (Nordland 9.2, Tromsoe 8.8, Finmarken 8.1), as well as some districts along the western coast and the fjords there (Hardanger only 7.0), and a few stray districts in the southern part.

The urban population of Norway represents, as has been said above, a rather small part of the entire population, smaller perhaps than in any other country in Europe. The cancer mortality is seen to be distributed between cities and rural districts

in about the same proportion, showing an excess of only 1.6 per cent against the urban population.

	POPULATION	CANCER MORTALITY
	per cent	*per cent*
Cities	28.9	30.5
Rural districts	71.1	69.5

It must be remembered, however, that the two largest cities, Christiania and Bergen, representing together about 42 per cent of the whole city population, show a lower cancer mortality than the average for the whole country; and that a considerable number of cities of 10,000 and more inhabitants also possess a cancer mortality not exceeding the cancer figure for all Norway, 10.7.

On the other hand, a number of small towns along the Skagerak coast (south) show very high cancer figures (from 14.0 to 25.8), perhaps because these places are largely inhabited by old, retired, sailors.

As a whole, though, it seems that town life in Norway does not especially favor the development of cancer; perhaps rather the contrary is the case.

3. *Carcinoma and sarcoma*

Of the whole number of deaths from malignant tumors (22,111), sarcoma accounts for 1185 (5.36 per cent), whereof 619 (52.2 per cent) are of males and 566 (47.8 per cent) of females.

There has been a slight variation in the frequency of sarcoma between single years within the period, from 4.35 per cent (1908) to 6.14 per cent (1905), though without any regular movement being discoverable. A similar variation can be noted among the counties during the whole period, from 3.34 per cent (Jarlsberg-Larvik) to 6.51 per cent (Nordland).

The highest percentage of sarcoma has, as a rule, been reported from the northern and western coasts, the smallest from the inland districts.

4. Distribution of malignant tumors as to sex and organs

The ratio as to sex will be seen in the following summary (1902–1911):

	MALES	FEMALES	TOTAL
Carcinoma	10,092 (48.5%)	10,724 (51.5%)	20,816
Sarcoma	621 (52.2%)	569 (47.8%)	1,190
Total	10,713 (48.7%)	11,293 (51.3%)	22,006
Population 1910	1,155,673 (48.3%)	1,236,109 (51.7%)	2,391,282
Individuals above 35 years of age	353,243 (45.6%)	421,510 (54.4%)	774,753

This makes it apparent that *malignant tumors in Norway are very equally distributed between the sexes,* all ages being taken into account.

With regard to ages above 35 years, there is some preponderance of carcinoma among males, and a somewhat greater one in the case of sarcoma.

The Norwegian mortality statistics up to 1910 have specified very inadequately the localization of carcinoma. Only the stomach, liver, genital organs (external and internal), and mamma have been specially mentioned. The following summary gives the figures for the years 1902–1911:

	MALES	FEMALES	TOTAL
Carcinoma			
Stomach	7,037	5,712	12,749
Liver	751	755	1,506
Sexual organs	125	1,343	1,468
Mamma	4	838	842
Other organs and unspecified	2,175	2,076	4,251
	10,092	10,724	20,816
Sarcoma			
Osseous system	258	197	455
Other organs and unspecified	363	372	735
	621	569	1,190
Total	10,713	11,293	22,006

The *predominance of gastric carcinoma* is very conspicuous—61.2 per cent of all carcinomas; furthermore, a majority of the liver carcinomas may doubtless also be added to this group. Carcinoma of the stomach is more prevalent among males, who furnish 55.2 per cent, while females contribute but 44.8 per cent. This excess among males is, in reality, still more prominent than it seems, for the number of males and females in Norway above 35 years has been found to be relatively 44.6 per cent and 54.4 per cent (census of 1910). Consequently, where 100 men above 35 years of age die from cancer of the stomach, only 68 women succumb to this disease.

For the year 1911, the diagnoses have been somewhat more carefully specified, accounting thus for carcinoma of the various internal sexual organs. One hundred and thirty-six cases of uterine cancer having been reported for this year alone (9.2 per cent of all carcinomas of the female genitals during the whole decade), it may be concluded that carcinoma of this organ will account for 80–90 per cent of all deaths from genital cancer in this country.

5. *Age*

The cancer mortality in Norway exhibits the same well known relation to age as everywhere else; only a very few cases occur in individuals below 20 years of age, after which there is a gradual increase in frequency through every decennium up to the higher age periods until the absolute maximum of deaths is reached at 60 to 70 years; thereafter a slow decline takes place. The relative maximum of deaths, however, is found in the group of 70 to 80 years, after which a decrease sets in.

For carcinoma alone the figures for the period 1902–1911 are given in the table below.

Whether this decline after the 70 to 80 period is real, or only apparent, is difficult to decide. But a great number of deaths from cancer among aged people is doubtlessly hidden under the diagnosis "senile debility," a diagnosis which plays a rather too prominent part in our mortality statistics, being second only, indeed, to that of tuberculosis.

AGE	NUMBER OF REPORTED DEATHS	NUMBER OF DEATHS PER 100,000 LIVING
20–30	108	3.23
30–40	586	21.25
40–50	2,067	91.79
50–60	4,498	231.65
60–70	6,183	443.03
70–80	5,610	680.11
80–90	1,790	549.90
over 90	88	289.00

The reports mention 21 deaths (0.95 pro mille) from carcinoma below the age of 20 years, but as it is not stated whether the diagnoses were based upon the findings at operation or post-mortem examination, or whether they were made from microscopical preparations, these cases can be accepted only with reservation.

6. *The relation between the number of aged people and the frequency of cancer*

The undeniable connection between advanced age and a predisposition toward cancer, gave rise to the idea that the wide variations in the number of cancer deaths in different districts might be brought into connection with similar variations in the numbers of aged persons resident in them. There might prove to be, in other words, a certain parallelism between the percentage of cancer deaths (the cancer-figure) and that of aged persons (the age-figure) in the various districts.

To test this theory, a calculation was made (national census of 1910) of the relative number of individuals above 35 years of age in the individual districts, as well as in the whole country.

It was found that 32.4 per cent of the entire population of Norway were of the said age, but that the percentage, the age-figure, varied for the districts from 42.5 (most aged population) down to 20.5 (young population), the variation of the age-figure in the towns being from 45.2 to 21.0.

A high age-figure is mostly found in the mountain regions, in the inner parts of the fjords, and in the agricultural districts;

also in a number of small towns along the southern coast (where old sailors are settled), the same towns in which the cancer-figure was shown to be high.

A low age-figure is very marked in all the northern parts of the country (in the plurality of the districts north of 65° N.L.), on some parts of the western coast, and in the great industrial centers.

To a certain extent, a coincidence of low or high age- and cancer-figures could certainly be noted. In the northern districts both figures are mostly low, while in the southern towns both are high; and a considerable number of districts and towns possessing age-figures of medium height also exhibited cancer-figures upon much the same level. But the expected parallelism between the two can not be demonstrated a ruling law; at both extremities of the scale the relations between the age-figures and cancer-figures may assume a rather paradoxical aspect, districts and towns with a low age-figure (young population) showing a very high cancer-mortality, and those with a high age-figure (aged population) being nearly exempt from cancer.

Consequently a direct connection between the number of individuals above the age of 35 years and the number of deaths from cancer in a given district can not be demonstrated.

II. THE MATERIAL COLLECTED BY THE NORWEGIAN COMMITTEE FOR CANCER RESEARCH, 1908–1912

The mortality statistics give at present the only reliable information as to the general frequency and the geographical distribution of cancer in Norway. But these statistics contain very little information, or none at all, regarding the distribution of the disease among different organs, among the various trades and occupations, and about the families, dwellings, etc. of the patients. At this point we must recur to the material gathered by the Norwegian Cancer Committee, though this being entirely dependent upon voluntary contributions from practitioners all over the country, has been forthcoming rather irregularly, and

does not allow of any immediate comparison with the official mortality statistics. This material, consisting of 4219 cases (living and dead), has some peculiarities.

Thus it shows a considerably greater surplus of females (57.5 per cent against males 42.5 per cent) than the official mortality statistics do; this is perhaps because of the frequently accessible localization of cancer in women (uterus and mamma, amounting to nearly 26 per cent of the whole collected material), which makes for easy diagnosis. Hence they are more often reported than cases of cancer affecting the stomach, say, which is the most frequent site in men.

1. Distribution of malignant tumors according to sex and to the organ involved

(The diagnoses concern only the primary localization).

	Males		Females			Total	Percentage of all cases reported
A. Carcinoma							
Cutis	131 (60.0%)	+	88	(40.0%)	=	219	5.2%
Labium	289 (88.7%)	+	37	(11.3%)	=	326	7.8%
Cavitas oris	95 (56.6%)	+	76	(43.4%)	=	171	4.1%
Oesophagus	56 (55.4%)	+	45	(44.6%)	=	101	2.4%
Ventriculus	747 (57.0%)	+	563	(43.0%)	=	1310	31.4%
Intestinum	142 (46.8%)	+	161	(53.2%)	=	303	7.2%
Hepar et cyst. fell	27 (37.0%)	+	46	(63.0%)	=	73[1]	1.8%
Pancreas	19 (59.4%)	+	13	(40.6%)	=	32	0.8%
Tractus respir	13 (55.0%)	+	11	(45.0%)	=	24	0.6%
Tractus urin	22 (50.0%)	+	21	(50.0%)	=	42	1.0%
Genit. externa	22 (35.0%)	+	41	(65.0%)	=	63	1.5%
Genit. interna	29 (5.5%)	+	499	(94.5%)	=	528	12.6%
Mamma	5 (0.9%)	+	539	(99.1%)	=	544	13.2%
Organa div	13 (27.0%)	+	34	(73.0%)	=	47	1.1%
	1610 (42.5%)	+	2174	(57.5%)	=	3783	90.7%
B. Sarcoma	165 (42.3%)	+	225	(57.7%)	=	390	9.3%
	1775 (42.5%)	+	2399	(57.5%)	=	4173	

A. Carcinoma. Carcinoma of the stomach, with 31.4 per cent of all cases, occupies first place also in these reports, even though it is only a little more than half as frequent as stated in the mortality statistics (61 per cent). It is somewhat surprising to find the rather rare primary cancer of the liver reported is as many as 55 cases (+ 18 cases of c. cyst. felleae), and it may be safely assumed that the great majority of these were primarily cancer of the stomach. In only 6 cases has the diagnosis of primary cancer of the liver been based upon laparotomy or autopsy, and microscopical examination. The frequency of cancer of the liver should accordingly not exceed 0.14 per cent.

In second place comes cancer of the internal and external genitals, and of the breast, comprising together 27.3 per cent of all reported cases, and showing in both groups an overwhelming majority of the cases in women.

The carcinoma of the external genitals ought, to a great extent, to be classed as cancer of the skin.

Cancer of the lip is much more frequent in males (88.7 per cent) than in females (11.3 per cent), the lower lip being the seat of the tumor in 95.7 per cent, the upper lip in 4.3 per cent only of the cases. This seems to strengthen the old suspicion against the tobacco pipe, and particularly the clay pipe, as the causal factor, the more so as lip-cancer in Norway is geographically almost exclusively limited to certain remote valleys and forest and fishing districts on the western coast, where the clay-pipe is still, perhaps, a favourite. On the other hand, only a very few cases of lip cancer have been reported as originating in individuals born and living in towns (mostly from Stavanger).

2. Distribution of carcinoma as to localization, sex, and age

Only 3785 out of the 4219 reports give the information necessary to a proper estimate.

More than 26 per cent of all these cases occur in the years from 60 to 69, and nearly 25 per cent in the 50 to 59 year group; consequently more than half of all cases are found in the 50 to 70 year group.

	Under 20		20-29		30-39		40-49		50-59		60-69		70-79		80-89		90 and more		Age not reported	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
1. Cutis	2		2	1	6	4	13	15	26	21	34	24	33	20	7	7			2	1
2. Labium			3	1	8	1	27	4	69	7	94	9	60	10	25	5			3	
3. Cavitas oris					3	2	12	15	17	21	36	22	20	13	5	3	1		1	
4. Oesophagus					4	4	6	3	15	8	14	14	14	11	2	4			1	1
5. Ventriculus			4	4	31	31	110	83	203	139	234	167	130	100	25	21	1	5	9	13
6. Tract.intestin.			3	2	4	6	14	23	32	37	53	50	23	28	10	10	2	1	1	4
7. Hepar					3	2		5	8	15	12	11	3	6	1	7				
8. Pancreas			1				4		6	4	5	4	3	4		1				
9. Tract. resp.					1	1	3		2	8	4	1	3	1						
10. Renl. Tract. urin.				1	1	3	6	2	5	6	3	5	4	3	2	1			1	
12. Genitalia ext.					2	4	1	8	6	9	4	10	9	8		2				
12a. Genit. int. viril.					3		1		6		5		10		1				2	
12b. Genit. int. femin.		4		27		66		147		137		75		28		2				14
13. Mamma				14		75	1	181		117	4	91		36		13		1		11
14. Diverse gland.		1		1	1	1	3	8	1	7	4	4	0	2						
15. Not localized.							2	3		4	2	2								1
	2	5	13	51	67	200	203	497	396	540	508	489	312	270	78	76	4	7	20	45
	7		64		267		700		936		997		582		154		11		65	

$$\underbrace{\text{m. } 1603 + \text{f. } 2182}_{3785}$$

The decade 60 to 69 years shows in both sexes the greatest number of carcinomas of the skin, lips, mouth, oesophagus, stomach and intestine, external genitals, and internal genitals in males.

On the other hand, the maximum for carcinoma of the internal female genitals, as well as of the breast, occurs as early as the 40 to 49 decade, and the frequency-diagram shows that cancer of the uterus and of the breast follow each other very closely throughout all ages, both reaching their climax during the forties. Cancer of the stomach in women, on the contrary, reaches its highest figure during the sixties.

This early appearance of cancer in the female generative organs may, perhaps, be connected with the earlier biological senility of these structures.

3. *Carcinoma in the young*

Carcinoma in persons less than 30 years of age has been reported in 71 cases (1.68 per cent)—15 males and 56 females. In young men, we find the tumor located in the skin (4 cases), stomach (4), lips (3), intestine (3), and pancreas (1). In young women, the localisation is most frequently in the internal genital organs (uterus, 18, adnexa 3, ovarium 12, = 33), and in the breast (14).

Up to the age of 25 years, only 24 cases are reported, as the following table shows:

	AGE																				TOTAL	
	14		15		18		19		20		21		22		23		24		25			
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Ovarium...........		1				2		1						1				1		2		8
Uterus.............														1		1				2		4
Mamma............										1		1								2	·	4
Cutis...............			1		1															1	2	1
Parotis............												1										1
Ventriculus........													1				1				2	
S. Roman..........									1												1	
Ren................												1										1
		1	1		1	2		1	1	1		3	1	2		1	1	1		7	5	19
	1		1		3		1		2		3		3		1		2		7		24	

It will be seen that only 8 cases are reported in patients under 20 years of age (3 males, 5 females); of these, two young men (of 15 and 16 years) suffered from carcinoma cutis nasi, and one from carcinoma S. Romani. Of the women, four had carcinoma ovarii and one carcinoma mammæ. These eight cases had all been verified by laparotomy on postmortem section, and microscopical examination.

B. Sarcoma. As seen in the table on page 116, the sarcomas

play a considerably greater part in these reports than in the mortality statistics, amounting to 390 cases out of 4219, or to 9.3 per cent as against 5.36 per cent. They show a preponderance in females (57.7 per cent), the figure for males being 42.3 per cent.

As usual, the sarcomas occur more uniformly within all age-groups, 23 cases (6 per cent) occurring in individuals under 10 years of age, though the fifties, with 64 cases (16.2 per cent), show the maximum incidence.

The sarcomas have in most cases developed from the skin and connective tissues (42 per cent), or from the osseous system (27.6 per cent). From the muscular system 9 sarcomas are reported, of which no less than 8 arose from m. rectus abdominis.

4. Multiple malignant tumors

In this category are included only those cases in which two or more malignant tumors have developed in the same individual, either simultaneously or successively, but both (or all) being of such a nature or appearing under such conditions that no connection could be found between them; in other words, none were metastases or recurrences.

Among the 4219 reported cases, 32 (0.76 per cent) multiple tumors were to be found, 31 double and 1 triple tumor. The combinations in which they occurred were as follows:

Carcinoma + carcinoma	25
Carcinoma + sarcoma	6
Sarcoma + sarcoma	1

The triple carcinoma had its localization in the stomach, the coecum, and the flexura coli d.

In 15 of the double cases, the first tumor observed developed from the squamous epithelium of the skin (9) and the lips (6). In 12 cases (6 from skin, 6 from lips) the second tumor also developed from the squamous epithelium, but only once was it so localized that a suspicion of direct inoculation might be justified (corresponding places on both lips); in this case, however, the first tumor had been extirpated 16 years before the second one appeared, and there had been no recurrence.

On the whole the length of time intervening between the first and the second of these skin and lip carcinomas was rather long, running from 3 to 25 years; in only two cases did the two growths appear within the space of two years.

Of the 5 cases of multiple tumors developing from the stomach and alimentary canal, 4 seem to have been simultaneous; in the remaining case there was an interval of only one year.

The 5 cases with two mammary carcinomata also exhibited both tumors almost simultaneously in both breasts, or within not more than 3 to 4 years.

5. The geographical distribution of the various cancer sites

This can not be sufficiently shown through these reports, as they have been forthcoming with too great an irregularity. It is nevertheless well known that cancer is found at widely different sites in different parts of the country. Thus Dr. Munch Soegaard and Dr. Garman Andersen found years ago that carcinoma uteri is exceedingly rare in the district of Hardanger, and it has already been mentioned that cancer of the lip is to a great extent limited to the remote valleys, to the highlands, and to some few districts on the south western coast.

6. The distribution of carcinoma of various organs according to social position and occupation

The social position and occupation, which have been reported in 2554 cases under about 80 different classifications, have here been collected into 9 groups, each containing from 1034 to 55 persons: (1) Farmers (1034); (2) factory employes (538); (3) skilled laborers (285); (4) female servants (205); (5) sailors and fishermen (176); (6) business men (129); (7) minor government and municipal officials (67); (8) teachers, telegraphers, etc. (55); (9) officials, officers, artists, university graduates (65).

The stomach, skin and lips, uterus, and mamma, have been considered according to the relative frequency with which they are involved in each of these 9 groups.

The percentage of cancer of the stomach to all cancers is:

	TOTAL	MALES	FEMALES
	per cent	*per cent*	*per cent*
Minor officials	62.7	88.6	34.4
Skilled laborers	57.2	83.3	30.8
Laborers	51.1	70.3	32.9
Farmers	48.5	56.3	39.0
Sailors and fishermen	43.7	76.2	25.7
Business men	38.8	81.6	20.8
Female servants	38.5		38.5
University men, artists	33.9	77.7	17.0
Teachers, etc	32.7	68.7	17.9

Carcinoma [cutis et] labii shows quite different figures, as follows:

	TOTAL	MALES	FEMALES
	per cent	*per cent*	*per cent*
Farmers	30.0	43.7	13.0
Laborers	17.8	29.7	7.2
Teachers	16.4	21.3	10.3
Sailors, fishermen	15 3	23.8	8.2
Skilled laborers	14.7	16.2	13.3
Minor officials	11.9	11.4	12.5
Officials, artists	9.1	22.3	4.3
Business men	7.0	17.4	2.2
Female servants	4.0		4.0

With the carcinomata peculiar to women we find that cancer of the uterus exhibits the following frequency:

	CALCULATED WITH REGARD TO WOMEN ONLY	FOR THE WHOLE GROUP
	per cent	*per cent*
Laborers	35.6	18.4
Sailors and fishermen	34.8	21.6
Minor officials	28.1	13.4
Female servants	27.3	
Skilled laborers	27.2	13.7
Business men	25.3	17.8
Farmers	17.1	7.5
Officials, artists	17.0	12.3
Teachers	10.3	7.3

Cancer mammæ showed on the other hand:

	WOMEN ONLY	FOR THE WHOLE GROUP
	per cent	*per cent*
Officials, artists	61.7	44.6
Teachers	61.5	43.6
Business men	51.7	36.4
Farmers	31.4	14.0
Sailors and fishermen	31.3	19.3
Female servants	30.2	
Skilled laborers	28.7	14.4
Minor officials	25.0	11.9
Laborers	24.3	12.6

The figures are much too small to allow of basing any conclusions on them, but they may perhaps give some hints.

Thus cancer of the stomach maintains its preponderance in men within all groups, though in the case of farmers, female servants, minor officials, and laborers, the women also are comparatively often afflicted. In these classes the women are constantly occupied with the preparing of food, and exposed to the effects of swallowing very hot foodstuffs.

Carcinoma (cutis et) labii shows a strongly marked predilection for farmers (lumbermen included). This points in the same direction as does the frequent occurrence of cancer on the under lip—towards the pipe, and particularly the clay pipe.

Carcinoma uteri finds most of its victims among the laboring, and seafaring and fishing classes, while mammary cancer seems most frequently to occur among the wealthier groups.

These suggestions are, however, offered with every reservation.

7. Heredity and infection

There are 2706 of the reports which give information as to the patient's family and domestic relations (parents, children, brothers and sisters, husbands and wives, persons living in the same house, neighbors, etc.). Of these, 1828 (67.5 per cent) deny the occurrence of cancer within this circle, while 878 (32.5 per cent) admit the presence of the disease, with the following distribution:

The patient's	Cases
Father was cancerous in	250
Mother was cancerous in	230
Brother or sister (513 individuals) were cancerous in	399
Children (24 individuals) were cancerous in	23
Of these	
Father and mother both were cancerous in	11
Father, brother, or sister was cancerous in	44
Mother, brother, or sister was cancerous in	42
Father, mother, brother or sister was cancerous in	6
On the other hand, cancer is reported in the patient's	
Husband or wife (*cancer à deux*) in	134
Others living in the same house in	174
Others living in the neighborhood in	224
Near friends in	228

The two groups last mentioned are, however, often rather vaguely defined. Now, all cancer patients have a father and a mother, but not all are married, a fact that of course will give some preponderance to the possibility of finding more cancer patients with cancerous parents than with cancerous mates. But of all the reported cases, only 17.4 per cent were unmarried, and even with addition of these 17.4 per cent double cancer is considerably rarer than cancer in the ancestors and descendants.

It may therefore be concluded that married life with a cancerous person does not seem to convey any greater risk of the development of cancer than does descent from a cancerous father or mother.

Experimental research has shown that a graft of cancerous material will, as a rule, develop in the recipient into a tumor of the same histological type as the original growth. Hence, if cancer in married couples depended upon direct inoculation, it might be expected that the same type of tumor would be found in the two connected cases. Of 125 cases in which this question could be investigated, both mates in 55 couples suffered from cancer of the stomach, in 3 couples from cancer of the lip, in 2 from cancer of the skin, and in 3 from sarcoma. In 63 cases the tumors in husband and wife differed in both type and localization. In no case was cancer of the external genitals found in both.

These figures do not give sufficient support to the supposition of the direct transfer of cancer from one person to another, the less so as the great majority of homogeneous double cases belong to the gastric carcinoma group, in itself so preëminently numerous that the probability of coincidence is great. Besides, married people will as a rule live under identical conditions and partake of the same food.

The reports on cancer affecting parents and offspring show that the localization of the tumors has been the same in all patients in 304 families numbering 667 patients. In the great majority (273 families) the stomach has been the site involved, several times with 3, 4, or 5, and once even with 6 cases in the same family. In 33 cases, cancer of the lip has been the family disease (once with four cases in the nearest family circle), and in 14 families, cancer of the skin.

Sometimes, also, rarer localization with two or more cases in the same family has been reported: carcinoma maxillæ sup. 6 times; c. cutis nasi 2 (in one of the families three members, two sisters and the daughter of one of them); c. canthi ext. 1; c. oesophagi 1 (in four members of the family); c. recti 3; c. vesicæ 1; c. uteri 9; c. ovarii 3; c. prostatæ 1.

In 417 families, on the other hand, embracing 883 cancerous individuals, the localizations were very varying, even twins of the same sex having cancers of different type.

Some of the cases here reported may, perhaps, point in the direction of a family disposition, possibly in the shape of an inherited tendency toward fetal dislocations in the sense of Cohnheim.

8. Special and local reports

From a number of practitioners living in the most widely separated parts of the country, the Norwegian Cancer Committee has also received special and detailed reports on the behaviour of cancerous diseases in their various limited regions. Some of these are of great interest but can not here be given. For example, it is not seldom reported that the population in certain circumscribed localities seems to be disproportionately afflicted

with cancer, without it being possible to discover any reason therefore; it has also been reported that the disease after a number of years has disappeared from such places. Again, from the far north, and particularly from Finmarken, several reports agree in stating that the Finlanders (Kvaens) and Lapps are comparatively less often attacked by cancer than the Norwegians themselves, and that immigrants especially from southern parts of the country seem to develop cancer when settling there.

SOME PHASES OF RADIUM ACTION WITH SPECIAL REFERENCE TO THE HEMATOPOIETIC SYSTEM

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HISTORICAL

Although a great deal of work has been done in demonstrating the effects on the hematopoietic system of exposure to the various radioactive substances, most of the conclusions reached have been based on the results of experiments on the lower animals, chiefly mice, guinea-pigs, and rabbits. The pioneers in this work were German. Thus, Heineke (2) first demonstrated the profound changes brought about in the spleen and lymph-nodes of mice and guinea-pigs by exposure to the Roentgen rays. No attempt, however, will be made to give a complete review of the voluminous literature: a good summary of all work done prior to 1913 has been provided by Gudzent (1). Suffice it to say that the chief results obtained have been from observations of Roentgen-ray effects, which may be summarised as follows:

1. Destruction of lymphoid cells and deposit of pigment in the spleen (2). The earlier of these effects is explosive in character, and precedes effects on any other group of body cells.
2. Destruction of all forms of bone-marrow cells *in situ* (3).
3. Primary rise of polymorphonuclear count, followed by a drop to a point below normal (4).
4. Steady decline in lymphocyte count (5).
5. Resistance of the red cells to radiation (5).

Although something is known in a vague way among the medical profession about blood-changes in roentgenologists, close

analysis shows that very few other investigations have been made in man, and deductions have sometimes been drawn from an altogether insufficient number of blood-counts. Allen (6), however, was able as early as 1903 to show an immediate slight leucocytosis following x-ray treatment without any appreciable effect on the red cells. Kolde and Martens (7), using mesothorium, demonstrated a primary drop in the red count followed by a return to normal on the fourth day. The most recent work is that of Schweitzer (8), who studied the effect of mesothorium treatment on the blood of patients suffering from cancer of the cervix uteri or vagina. The dosage used was from 2600 to 7700 milligram-hours. His counts were made daily at the same hour and are, therefore, strictly comparable. No counts were made immediately after the application of the mesothorium. His findings may be summarised as follows:

1. Primary leucocytosis followed by a drop to below the original level within twenty-four hours. This subnormal level was maintained until eight weeks after the last treatment.
2. Primary drop in lymphocytes, followed by lymphocytosis.
3. Absence of effect on the red blood cells.
4. Changes in the eosinophile count similar to those in the lymphocyte.

It was this paper which stimulated us to attempt a somewhat more elaborate study of the effects of radium in similar cases, in the hope of throwing some light on the mode of action of the radioactive substances. Schweitzer attributes these blood changes to the action of a supposed "Roentgen-toxin" or to the production of toxic substances of unknown origin, and regards the leukopenia as an unfavorable effect.

INTRODUCTORY

The object of the following study was to determine the immediate and remote effects of radium on the activity of the blood-forming organs, as demonstrated by the numbers of the various formed elements found in the circulating blood at definite stated intervals after the radium application, and with special reference to changes in the leucocytes.

For this purpose, ten patients were chosen who had squamous-cell carcinoma of the cervix uteri and vagina, some hitherto untreated, others with recurrences after a previous operation. The number of applications varied in the different cases, as did also the intervals between applications. Some of the patients received *x*-ray treatment in addition to radium. In view of this fact, the remote effects of treatment may be due to the cumulative effect of both *x*-ray and radium. The immediate changes, however, following radium application may be ascribed to this agent alone, especially since these changes were present in most marked degree in those patients who had had no previous *x*-ray treatments.

TECHNIQUE

The radium was applied directly to the tumor mass in a brass cylindrical applicator,[1] which, for purposes of cleanliness, was wrapped in a rubber finger cot. No further screening was used. The applicator was introduced through a speculum and packed in place with cotton. In applications to the vaginal wall the healthy sides were protected by placing the applicator in a half-cylinder of lead 2 mm. in thickness, adhesive plaster and rubber being used to absorb the secondary rays.

The dose employed was 50 mgm. radium element in the form of radium bromide. The time used was thirty hours for each application whose immediate effects were studied, with two exceptions (case I, August 4, 1916, eighteen hours, and case VIII, November 20, 1916, twenty-six hours). Applications whose immediate effects were not studied varied from three to forty-eight hours in duration. The interval between treatments varied from twelve to sixty-two days, the usual interval being two to three weeks.

The patients were kept in bed during the whole course of the treatment. On the first day of the application the blood was counted in the early morning, between 5 and 9 a.m., usually at 5.45 a.m. The radium was applied immediately afterwards and

[1] The brass cylinder was the usual type distributed by the Radium Chemical Company of Pittsburgh, Pa., and styled "Universal Applicator. Type B."

counts were then made at the following intervals: $\frac{1}{2}$ hour, 1 hour, 2 hours, 4 hours, 6 hours, 9 hours, 12 hours, and then daily. The patient was given no breakfast, and took a light luncheon after the 6-hour count, and supper after the 12-hour count, so that there was always two and one-half hours between any meal and the next following blood-examination. The daily counts were made between 10 a.m. and 11 a.m., three or four hours after breakfast. The following counts were made on each occasion: Total white count and differential count (stained smear or unstained specimen used for white count[2]); in five cases a red cell count was also made (nos. VI, VII, VIII, IX, and X) and in three a platelet count (nos. VI, IX, and X).

Observations on any given series were made as far as possible by a single individual in order to eliminate individual differences in technique.

TREATED PATIENTS

The following changes were found to take place in the period immediately following the radium application.

A. Total white count

1. A drop in the total white count. This usually was found to occur within the first half-hour, but sometimes did not reach its lowest point until six hours after the radium application. In one instance no drop was recorded, but here the half-hour count was not taken (case IX). Counts made on this patient during a subsequent treatment showed a primary drop during the first half-hour. In two cases (VIII and X) the drop was preceded by a slight temporary rise. In one case (V) the primary drop was succeeded after a temporary rise by a secondary drop, which reached its lowest point six and fifteen hours after the application during two successive treatments.

[2] It was found by careful comparison of several simultaneous counts that there was usually no difference worth consideration between results obtained from stained and those from unstained specimens. Occasionally the difference was fairly distinct, but this did not occur more frequently than it does in counting two separate hundreds in one stained specimen.

2. A return of total white count to approximately its former level. This occurred on nine occasions within the first six hours, on seven occasions between six and twelve hours, and on two occasions between twelve and nineteen hours after the application.

3. A compensatory rise of the total white count, in some instances to a point considerably higher than before the radium application. This phenomenon occurred as follows:

Twice, two to three days after the application.

Three times, twenty-four to twenty-six hours after the application.

Four times, twelve to twenty-four hours after the application.

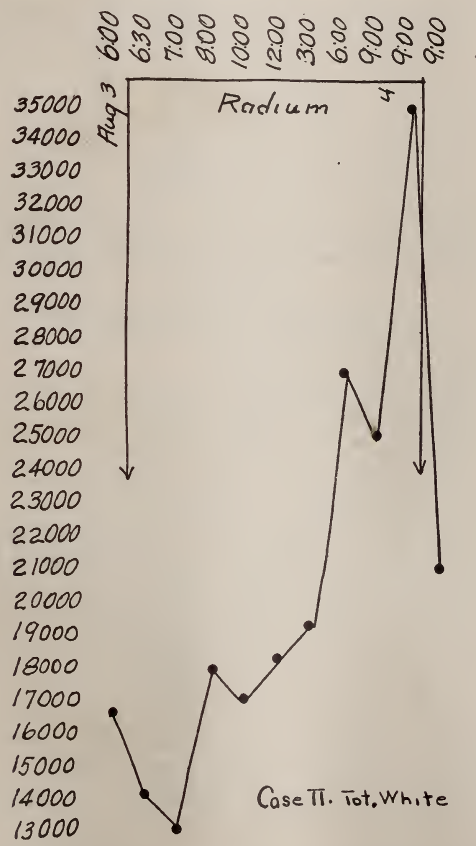
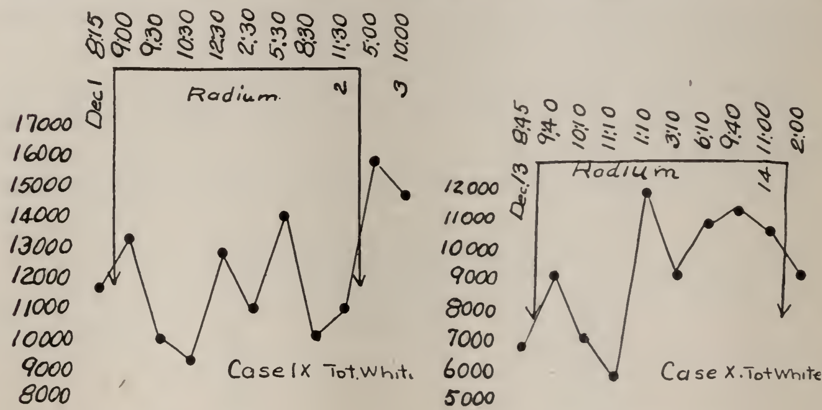


Chart 1. Early Changes in Total White Count

Twice, within twelve hours after the application.

Seven times, no such rise occurred.

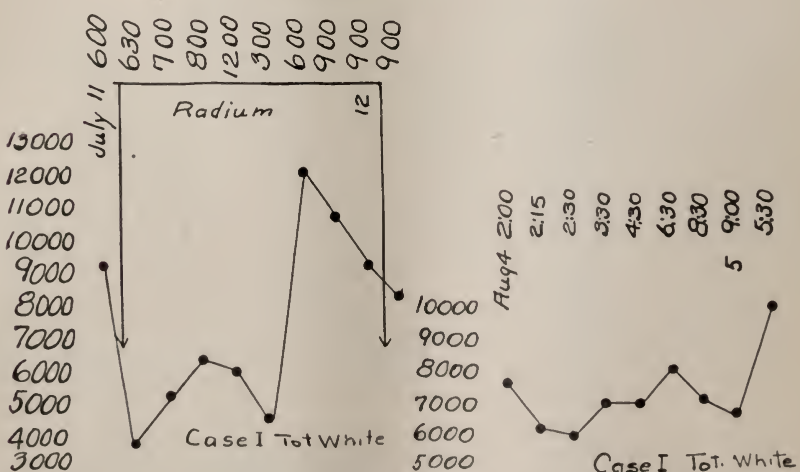
Another striking point that comes out on study of the charts is that in cases where the early response to radium application is not altogether typical, for example, when the primary drop in total



First treatment Second treatment

Charts 2a and 2b. Atypical Reaction Repeated During Subsequent Treatment

Note preliminary rise before usual fall



First treatment Second treatment

Charts 3a and 3b. Modified Reaction of Total White Count During Subsequent Treatment

white count is delayed, or unusually well sustained, or preceded by a temporary rise, the same behavior is noted during a later application (see cases V, VIII, and X).

Finally, it is also worthy of note that in one case (case I) the response of the polymorphonuclears to the radium application was not so marked following the later application as it was following the first. It would seem in this case that the power of the hematopoietic system to react to what would usually be an efficient stimulus had been diminished, either by frequent radium applications in the past or by the advance of the disease itself.

Observations on the stained smear, which will be considered later, seem to show that this failure to react is due to lasting damage to the hematopoietic system from the primary radium application.

B. Total polymorphonuclear count

This ran throughout so closely parallel to the total white count that all that has been said above in regard to changes in the total count applies also to changes in the polymorphonuclear count.

C. Total lymphocyte count

1. No characteristic change was found to occur in the total lymphocyte count immediately after the application of radium. There was more frequently a drop than a rise, but the degree of change in either case was usually so slight and the duration of the change so variable that it need not be considered.

2. No characteristic change in the total lymphocyte count could be demonstrated to occur during the first two weeks following treatment. The largest drop was from 7800 to 1000 (case IV) at the end of nine days, the largest rise being from 1200 to 4200 at the end of thirteen days (case VI).

3. In most cases, the total lymphocyte count varies to some extent in harmony with the variations of the total white count. This behavior is most noticeable, as a rule, when the variations in the total white count are considerable (cases III and IV), although it is sometimes noticed when variations are rather small

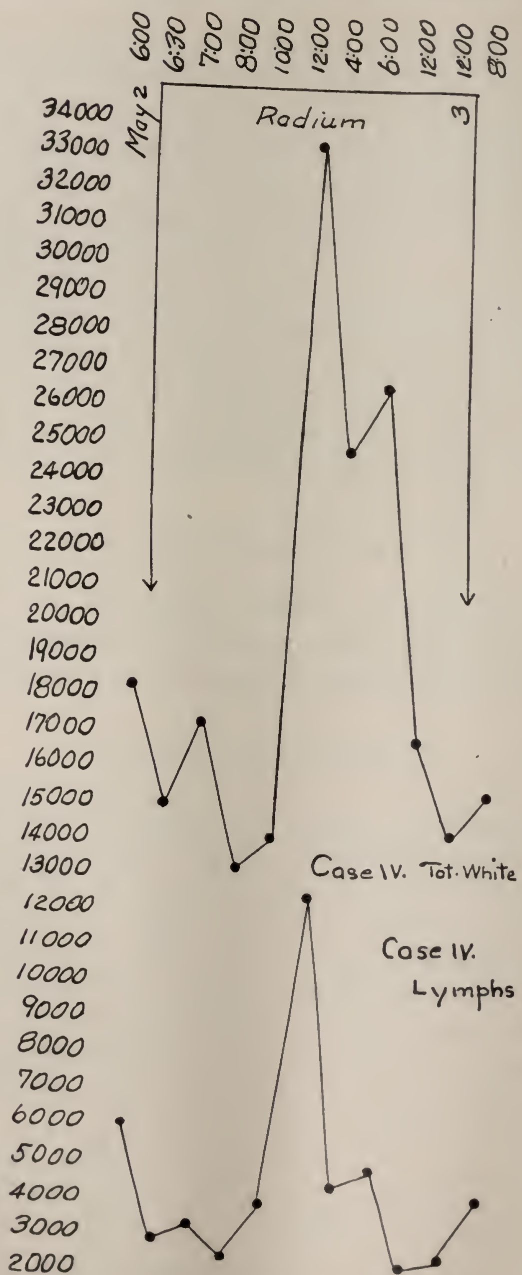


CHART 4. SHOWING EARLY CHANGES IN TOTAL LYMPHOCYTE COUNT COMPARED WITH CHANGES IN TOTAL WHITE COUNT

(case V). There are exceptions, however, to this general statement, as for instance in case VI, where the variations in the total white count are distinct, while the total lymphocyte count shows only a slight variation from one time to another.

D. Total large mononuclear count

No constant variations were found in the total mononuclear count.

E. Percentage values of the various cells

These were studied in stained smears made during and after nine radium treatments in five patients. In all these cases the blood showed some pathological findings before treatment was begun, as, for instance, absence of eosinophiles, immature forms of white and red cells, and changes in the form of the red cells. In two patients the percentage of polymorphonuclears and lymphocytes was within normal limits: in the other three there was pronounced neutrophilia and lymphopenia.

1. Neutrophiles. In eight out of the nine treatments there is first a drop in the neutrophilic curve, preceded in five instances by a brief preliminary rise lasting from one-half hour to nine hours after the radium application. This drop lasts from one to twelve hours after the beginning of treatment, and is immediately followed by a rise to a point which is always above the level noted before the treatment was begun, in some instances as high as 93 per cent. This rise usually attains its highest point within forty-eight hours after the time of application, though in one instance this was not reached until the third day. During the days that follow there is a gradual return of the curve to its normal level, which is usually reached by the fifth to the eighth day. In one patient (case X) the drop continued until the second treatment was begun (eleven days) and then continued still further until well below the normal level.

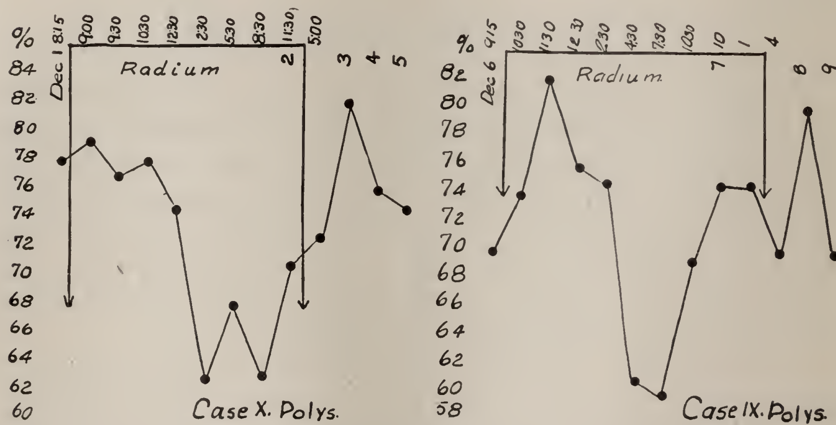
In one treatment no definite change in the neutrophile percentage could be demonstrated. This case showed a very pronounced neutrophilia and lymphopenia.

To summarize, the following points may be made:

(1) There is a drop in the neutrophile percentage, sometimes preceded by a temporary rise. This drop is not below the lower limit of normal.

(2) After twelve hours, there is a compensatory rise to a point above the upper limit of normal.

(3) The curve returns to the normal level in five to eight days.

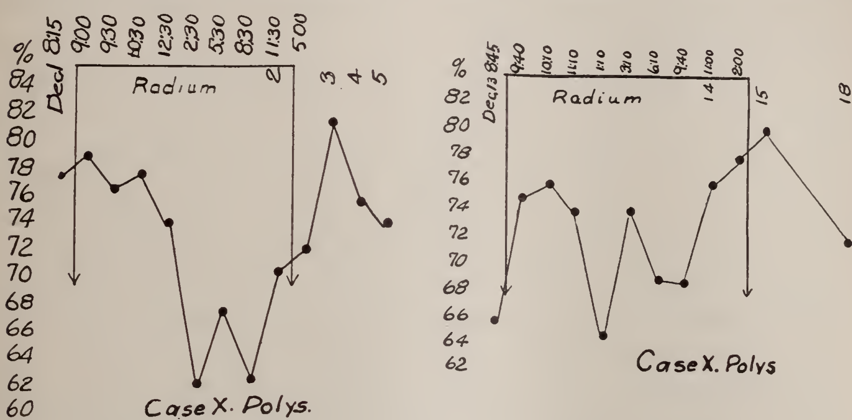


Charts 5a and 5b. Early Changes in Polymorphonuclear Percentages.

Of interest in this connection is the behavior of the myelocytes and of those neutrophiles which are in the transitional stage between the myelocyte and the polymorphonuclear form—the so-called "metamyelocytes" of Pappenheim (9). These latter cells could be demonstrated in the blood of all the patients before treatment was begun, indicating, probably, some irritation of the bone-marrow due to the toxins resulting from the disease. During radium treatment, however, they showed a decided increase simultaneous with the rise in neutrophile percentage. In cases VII and X the rise in metamyelocytes preceded and heralded the rise of neutrophiles. The myelocytes, likewise, were observed to increase in numbers. In four out of the five patients these were demonstrated in the blood in small numbers before treatment, but during treatment they were found much

more frequently. This was especially the case in case X, who, during her second treatment, showed 2 per cent myelocytes in the blood. It would seem, then, that the radium has a definite irritant action on the bone-marrow.

The behavior of the neutrophile count during subsequent treatments is somewhat modified. Four out of the five patients were given several treatments. Of these case IX showed simply an irregular drop in neutrophiles during the second treatment. Case VI, who was treated five times, and whose blood was studied



First treatment — Second treatment

Charts 6a and 6b. Changed Reaction of Polymorphonuclears During Subsequent Treatment

during the first and fourth treatments, showed no appreciable change in the neutrophile curve during the fourth treatment. It is fair to state in this connection that at this time she showed a marked neutrophilia (93 per cent) and lymphopenia (5 per cent). In case X the effect on the curve was not quite so marked during the second as during the first treatment.

In general, then, it may be said that the radium effect is more marked during the first application than during later treatments.

2. Lymphocytes. These likewise showed a constant percentage curve in eight out of the nine treatments studied. In case X no such response could be demonstrated, although even here

the curve has one thing in common with those of the other cases, namely the drop in relative lymphocyte count at the end of the 30-hour treatment. The changes noted in the other eight instances are as follows:

(1) An increase in the count, reaching its maximum in from two to twelve hours, and preceded in five instances by a brief preliminary drop. In the two cases which showed a normal percentage before treatment the count rose to 30 per cent, while in those which had showed marked lymphopenia the highest point never exceeded the upper limit of normal, and in some instances did not reach the normal level at all.

(2) After from four to twelve hours there begins an irregular drop, which in seven instances reaches its lowest point before the end of the treatment (thirty hours). In one instance, the lowest point is not reached until the next day, while in the ninth instance (case IX) the drop continues for eight days. In every instance the low point is well below the lower limit of normal. In those patients who showed a normal blood picture before treatment the percentage fell as low as 9 per cent, while in those with previous lymphopenia it even reached 4 per cent. In one case the low point was still slightly above the level noted before treatment (case VI, second treatment), but the blood in this case was highly abnormal, showing an extreme lymphopenia (5 per cent) before treatment.

It seems reasonable to infer that this drop in the percentage of lymphocytes is an expression of actual damage done to the lymphatic system, a supposition which is borne out by the finding of numerous pyknotic and vacuolated lymphocytes in the blood-smears taken during this period. These degeneration forms first appear six to ten hours after the beginning of treatment and remain in the smear until its end (thirty hours), an observation which agrees with those of Heineke (2).

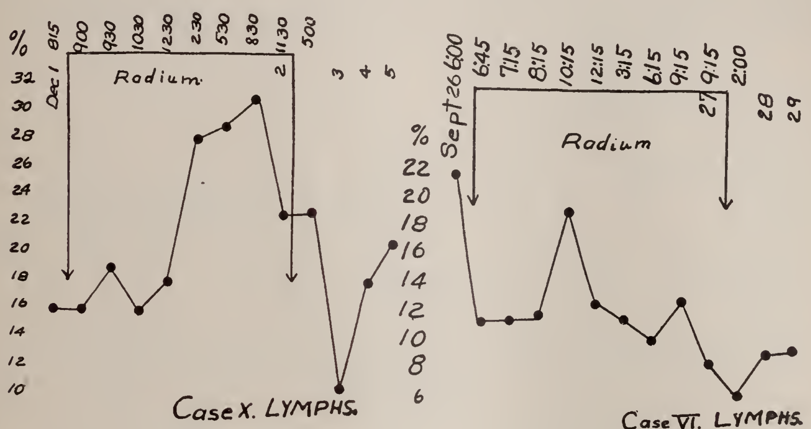
(3) Immediately or shortly after this period of depression there is a secondary rise in the lymphocyte curve, even in those cases which had showed a marked lymphopenia. In six instances this rise continues to a point slightly above the level noted before treatment, once to a point just below it. In one case only (case VI) it is impossible to demonstrate this rise.

To sum up, the lymphocyte curve is approximately the reverse of the neutrophile curve, and shows:

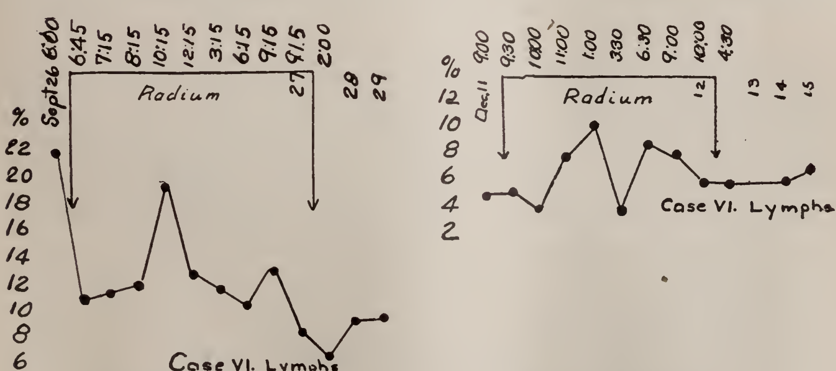
(1) A rise, sometimes to a point as high as 30 per cent, and preceded occasionally by a preliminary drop.

(2) A sharp drop after four to ten hours to a point well below the normal level.

(3) A return to the original level after several days.



Charts 7a and 7b. Early Changes in Lymphocyte Percentages Immediately Following Application



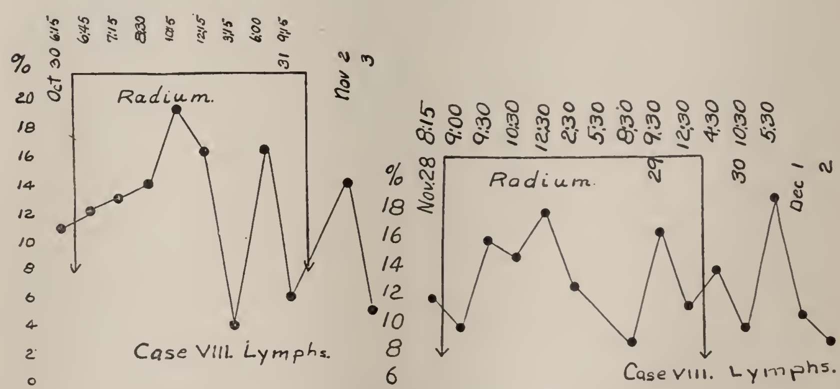
First treatment Second treatment

Charts 8a and 8b. Changed Reaction of Lymphocytes During Subsequent Treatment

As in the case of the neutrophiles, the lymphocytes show a modified reaction to repeated treatments. More than one treatment was given in cases VI, VIII, IX, and X.

In case VI, five treatments were given and the blood was studied during the first and fourth. The influence of the fourth treatment was much less marked than that of the first.

In case VIII the curve showed about the same course during both treatments, although the difference between highest and lowest points is less during the second than during the first.



First treatment

Second treatment

CHARTS 9A AND 9B. MODIFIED REACTION OF LYMPHOCYTES DURING SUBSEQUENT TREATMENT

In case IX, however, the influence of the second treatment was more protracted and intense than that of the first. The difference between high and low points was greater during the second treatment, the figures being 32 vs. 8 as opposed to 27 vs. 9 during the first treatment. After the first treatment the original level was again reached after forty-eight hours and the following weeks showed a rise in average lymphocyte count, while after the second the normal level was not reached until the twelfth day, and the average count of the following weeks (21 per cent) was less than the average count of the weeks following the first treatment (24 per cent). In this case, however, constitutional effects must be taken into consideration, because twenty-one

days after the second treatment there appears a terminal sharp drop in relative lymphocyte count.

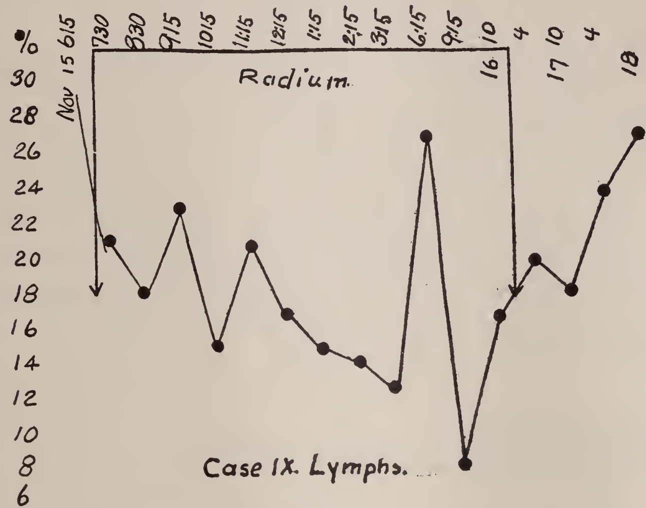


CHART 10A. INTENSIFIED REACTION OF LYMPHOCYTES DURING SUBSEQUENT TREATMENT
First treatment

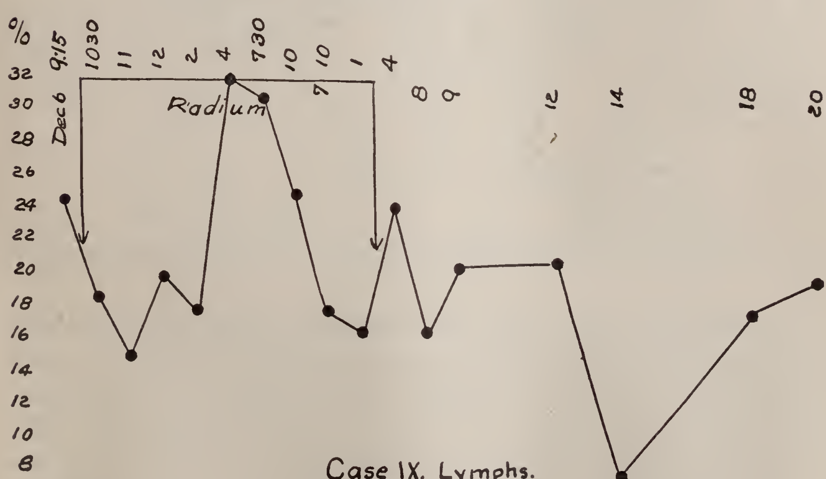
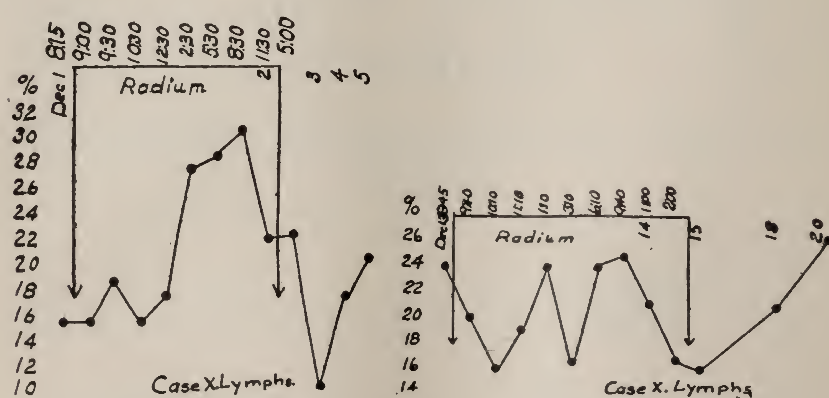


CHART 10B. INTENSIFIED REACTION OF LYMPHOCYTES DURING SUBSEQUENT TREATMENT
Second treatment

In case X the reaction of the lymphocytes to the treatment is decidedly stronger during the first application than during the second, as evidenced by these figures:

		per cent
First treatment	Highest	31
	Lowest	11
Second treatment	Highest	24
	Lowest	16

As in case IX, however, the effect is more protracted after the second treatment than after the first, the original level being again reached on the second day after the first treatment and not until the seventh day after the second. In the period following these treatments the count rose to 24 per cent after the first, and 26.7 per cent after the second.



First treatment | Second treatment

Charts 11A and 11B. Modified Reaction of Lymphocytes During Subsequent Treatment

In general, then, it may be said that the lymphocytic reaction, numerically considered, is less marked with subsequent treatments than with the original one, although the "depressor" effect may be more lasting after the later treatments. This fact seems to indicate a permanent damage to the lymphopoietic system from the first treatment, rendering it incapable of its normal reaction to a given stimulus and slower to recover from the effects of that stimulus. In cases VI and X there were

greatly increased numbers of pyknotic and vacuolated lymphocytes during the later treatments, which may be taken as confirmatory evidence of the increased damage to the lymphopoietic system.

3. *Large mononuclears.* During seven treatments there was noted a preliminary rise of the large mononuclear percentage, the highest point being reached four to twenty-six hours after the application. In three instances during a first treatment and

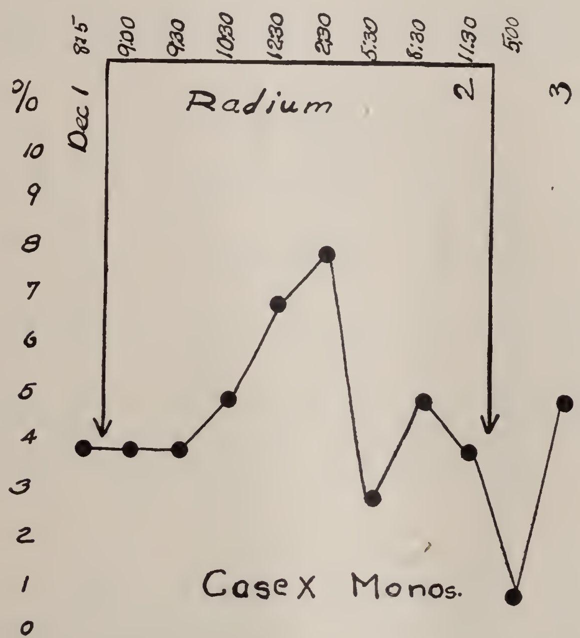


Chart 12. Early Changes in Mononuclear Percentages

once during a later treatment the figure rose above the upper limit of normal, but in all other instances the percentage remained within normal limits. This rise was followed by a drop which persisted until the end of the treatment on the day following. In two instances it continued to the third and fourth day respectively. Twice this secondary drop occurred without any preliminary rise. In all cases the curve fell to a point well below normal, once even getting down to 1 per cent. This drop

in turn was followed by a rise to the original level or above, lasting from one to nine days after treatment.

Repeated treatments showed absence or diminution in intensity of this effect. The curve of the large mononuclears follows so closely that of the lymphocytes as to favor the theory of their lymphatic origin.

4. Eosinophiles. Prior to treatment all patients showed an absence or decrease in number of the eosinophiles. During treatment there was noted in three cases a rise at varying periods, in one instance as high as 6 per cent. In the other cases no defi-

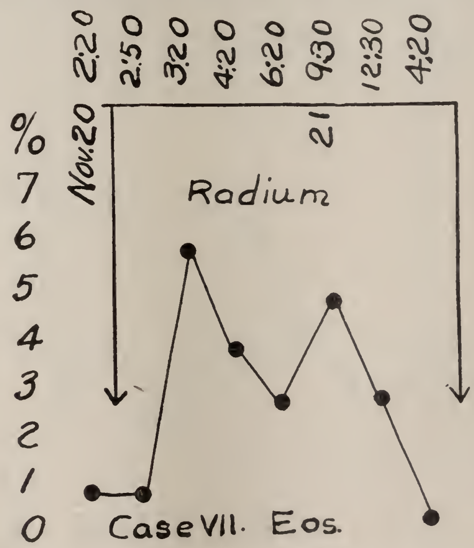


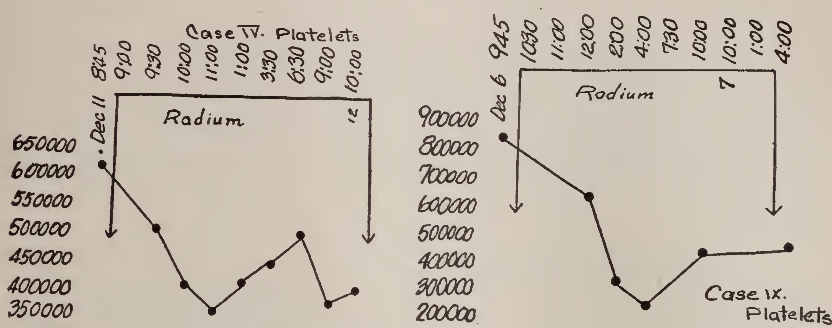
Chart 13. Early Changes in Eosinophile Percentage

nite influence was demonstrable. These findings are directly contrary to those of Schweitzer (8), who noted a disappearance of eosinophiles during and after treatment, with reappearance two to three weeks later.

F. Platelet count

The platelets were counted during four treatments on three patients (VI, IX, and X). In three instances there was an immediate drop; in two of these the drop was distinct and

lasted two and six hours respectively; in the third case the drop was very slight, lasting only an hour, and was succeeded by a slight steady rise for the succeeding two days. In one instance there was practically no change, although there was a slight steady drop for the first nine hours followed by a return to normal.



CHARTS 14A AND 14B. EARLY CHANGES IN PLATELET COUNT

In general, then, it may be said that the platelets, like the polymorphonuclear cells, show a tendency to an immediate though often a slight decrease in absolute numbers.

G. Hemoglobin

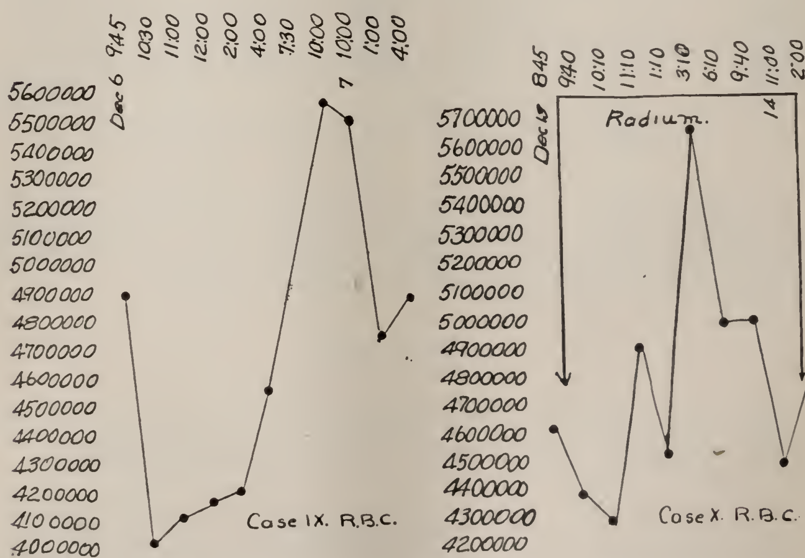
This was estimated on four occasions (cases VI, VIII, IX, X) during treatment, but showed no change of any importance.

H. Red cell count

The red cells were counted during seven treatments in five cases; in every instance there was considerable fluctuation in the figures. All cases, however, showed a definite increase in the count, at some period within the first three days following the time of application, to a level well above that of the count taken before the radium was applied. Thus:

CASE	BEFORE TREATMENT	LENGTH OF TIME	HIGHEST COUNT
VI	3,250,000	3 days	4,000,000
VII	4,300,000	22 hours	5,350,000
VIII	5,000,000	33½ hours	6,100,000
VIII	4,900,000	12 hours	5,600,000
IX	4,150,000	12 hours	5,000,000
IX	4,600,000	6 hours	5,800,000
X	4,500,000	½ hour	5,100,000

In five out of the seven instances there was a preliminary drop in the count, lasting from one-half hour to four and one-half hours in the different cases. This was especially marked in case X, which did not show so evident a secondary rise as the other cases.



Charts 15a and 15b. Charts Showing Changes in Red Blood Count
Specimen Charts

I. Blood-pressure

Blood-pressure estimations were carried out simultaneously with the blood-counts in five instances (cases VI, VII, VIII, IX, and X) with the idea of trying to determine whether any

evidence could be found for the formation of any substance having a lowering effect on the blood-pressure. Cholin has been shown to be one of the products of radium action and has been supposed by some authors to be responsible for the beneficial effect of radium on tumors (10). This substance exerts a depressor effect when introduced into the animal organism. The following table will show the results noted:

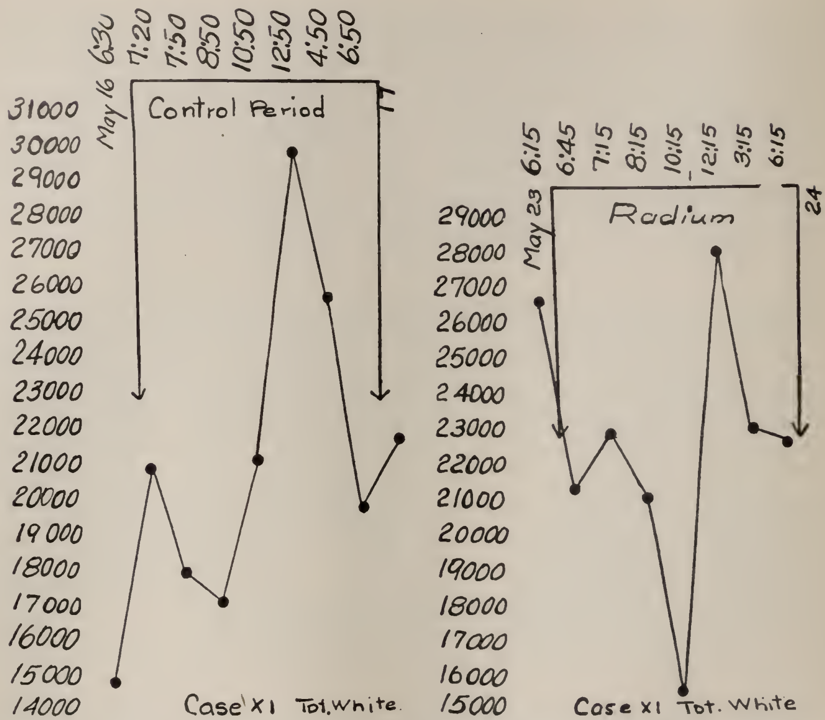
Blood-pressure readings—systolic and diastolic

TIME OF READING	CASE VI	CASE VII	CASE IX	CASE XB	CASE XA	CASE VIII
Before treatment	148–82	148–84	152–88	112– 80	122–86	114–68
½ hour after application	136–68	150–86	142–82	110– 82	120–88	112–68
1 hour after application	130–66	138–80	126–78	114– 86	126–90	110–66
2 hours after application	142–80	142–78	136–80	110– 80	114–86	116–66
4 hours after application	130–66	140–76	144–78	116– 86	122–90	116–68
6 hours after application	134–66		136–76	112– 80	120–82	114–66
9 hours after application	128–66		140–84	120–100	126–86	120–70
12 hours after application	128–66		138–84	116– 90	112–80	122–78
18 to 25 hours after application	122–64	130–78	136–82			120–68
26 to 36 hours after application	132–68	138–80	132–78		126–86	106–66

From this table it will be seen that in cases VI and IX, and to a less extent in case VII, there is a tendency towards a fall in blood-pressure. The others, however, show no such tendency. It seems fair to assume that the small drop noted in the three first cases may be explained as the result of complete rest in bed, especially as the three patients in question were ambulatory at the time of treatment while cases VIII and X were bedridden.

CONTROL CASE

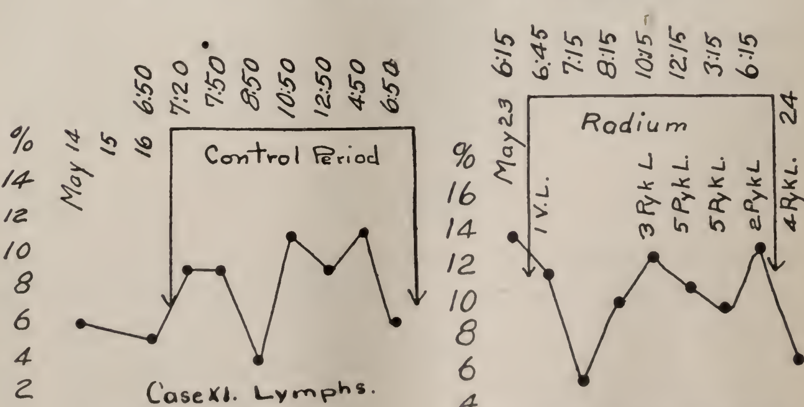
In order to control these observations, we selected an eleventh patient who also had an inoperable carcinoma of the cervix uteri, and counted her blood under exactly the same conditions as prevailed with the treated cases. While there was considerable fluctuation in the counts during the day, the features noted above were not reproduced. Thus, for instance, we find no initial drop in the total white count during the con-



A. Before any treatment (Control period)

B. During radium application

Charts 16A and 16B. Changes in Total White Count



A. During control period

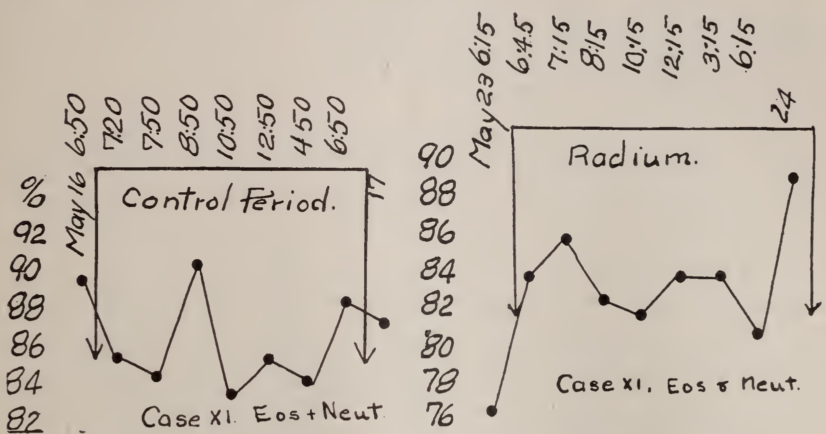
B. During radium application

Charts 17A and 17B. Changes in Lymphocyte Percentage

Note: V.L. = Vacuolated lymphocyte; Pyk.L. = Pyknotic lymphocytes

trol period, while during the radium treatment the usual curve is noted.

In a similar way, the percentage counts of lymphoid cells



A. During control period B. During radium application

CHARTS 18A AND 18B. CHANGES IN POLYMORPHONUCLEAR PERCENTAGE

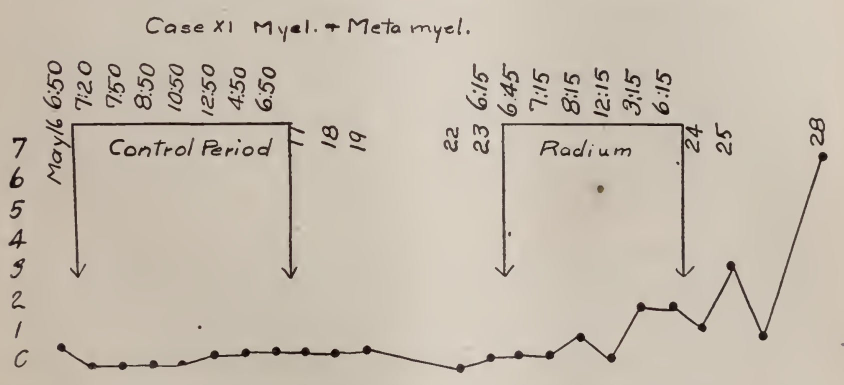


CHART 19. COMBINED MYELOCYTES AND METAMYELOCYTES DURING CONTROL PERIOD AND DURING RADIUM TREATMENT

and polymorphonuclears show no characteristic reaction during the untreated period, while during the radium treatment the typical curves are reproduced.

Most striking of all is the number of myelocytes and metamyelocytes found during radium treatment, as contrasted with their absence during the control period (see chart 19).

It is further noteworthy that pyknotic lymphocytes were abundant during the radium treatment, indicating destruction of the lymphoid elements, and completely absent during the control period (see chart 17B).

From a study of this case, therefore, it would seem fair to assume that the changes noted are indisputably dependent on the action of the radium, and not mere variations within physiological limits.

The remote effects of radium treatment as shown by the counts made on these nine patients may now be analysed. For the purpose of avoiding false deductions, the cases will be divided into those which were treated with radium alone (group 1) and those which had x-ray treatments in addition (group 2). In the former class there were three patients in the group studied: two of these were followed for only twenty-four and forty-six days respectively, but the third was followed up till the time of death.

In the latter class there were six cases: of these one was followed for thirty-four days, one for fifty-four days, one for fifty-seven days, and the remaining three until the time of death.

All intervals will be reckoned from the date of the first radium treatment, irrespective of whether that particular treatment was used for the purpose of studying the immediate blood changes.

In the following tables the blood changes are summarised by charting the various counts at arbitrary intervals. Unless otherwise stated the figures given are the average figures calculated from two to five counts on successive or almost successive days. This procedure was adopted to avoid the possibility of recording some single atypical count as representing the average count of the period. In some instances, only one count was made at a given period, so that sometimes it has been impossible to take the average of several counts. These instances are noted.

Tables Showing Remoter Blood-Changes Following Radium Treatment[3]

Group 1

CASE III	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment..............					
3 weeks after..................	11,000	7,600	2,100	69	19
4 weeks after..................	10,000[1]	8,400[1]	1,200[1]	84[1]	12[1]
5 weeks after..................	12,000	9,850	1,500	82	12
6 weeks after..................	8,500	4,500	2,400	53	28

In this group of cases the blood-changes may be summarised as follows:

Case III. (1) A slight decrease in the total white count, most marked at the end of six weeks.

(2) A sharp change in the relative polymorphonuclear and lymphocyte count from four to five weeks after treatment, due chiefly to a marked decrease in the absolute lymphocyte count.

(3) A reversal of this process at the end of six weeks, with marked decrease of the absolute and relative polymorphonuclear count and increase of the absolute and relative lymphocyte counts to a point slightly above normal. Comparison of these figures with those of three weeks previous shows the change to be primarily due to a depression of the polymorphonuclear count rather than to a lymphocytic increase.

To summarise the findings briefly, it appears that there was in this case first a depression of the lymphocytic series lasting from four to five weeks after treatment, and later a depression of the polymorphonuclears, appearing first after six weeks and accompanied by a recovery of the lymphocytic series.

Case IV. (1) A moderate decrease in the total white count, the lowest point being reached in four weeks, after which time the count begins to rise again.

[3] Blood-counts marked with the figure 1 throughout these tables are single counts. All others represent an average drawn from two or more counts on successive or almost successive days.

CASE IV	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	19,500	12,000	4,700	67	24
2 weeks after	13,500	7,800	3,600	58	27
3 weeks after	13,000	8,200	3,650	63	28
4 weeks after	10,000	5,300	2,800	53	28
5 weeks after	13,000	9,000	2,750	69	21
6 weeks after (approximately)	15,000	11,000	2,700	73	18

(2) A steady decrease in the total lymphocyte count, the percentage count increasing slightly for four weeks and then beginning to drop. In this case the fall in total lymphocytes during the first four weeks is not nearly so marked as the fall in the polymorphonuclear count and is roughly proportional to the fall in the total white count. Furthermore, during the fourth to sixth week the decrease in the total and relative lymphocyte counts is subordinated in importance to the rise in the polymorphonuclear count.

To summarise, this chart shows a primary depression of the polymorphonuclear count lasting four weeks, followed by a compensatory stimulation. Accompanying this effect there is a slight but progressive depression of the lymphocytic series, reaching the lowest point at the end of six weeks. These findings are a contrast to those noted in case III.

CASE VI	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	29,000	23,200	4,300	80	15
2 weeks after	33,500	28,100	3,350	84	10
1 month after	21,000	17,500	2,500	83	12
1½ months after	18,000	15,300	1,980	85	11
2 months after	28,000	23,250	3,400	83	12
2½ months after	20,500	17,800	2,050	87	10
3 months after	31,000	28,850	1,250	93	4
3½ months after	50,000	49,000	500	98	1
4 months after	130,000	127,400	1,625	98	1

Case VI. (1) A fall in the total white count and the total polymorphonuclears during the first one and one-half months

after a brief preliminary rise, followed by an irregular slight rise until three months and a sharp terminal rise from three and one-half to four months.

(2) A steady drop in the total lymphocyte count and a more gradual drop in the percentage count. The steady fall is interrupted at two months by a temporary rise in the total count, but at this period the rise in the total white count is proportionally almost as high.

(3) While at two and one-half months there is a temporary decrease in the total polymorphonuclear count, the rise in the polymorphonuclear percentage begins at that time and presages the later rise in the total polymorphonuclear count.

To summarise, then, we have in this case a drop in all white blood cells in about the same proportion during the first one and one-half months. The lymphocytic drop, however, starts at two weeks, the polymorphonuclear drop at one month. After the first one and one-half months there is a further decrease in the lymphocytes and a disproportionately large increase in the total white count and polymorphonuclears, ending in an enormous leucocytosis during the two weeks preceding death.

DISCUSSION OF RESULTS

Group 1

The remoter changes in blood-findings may be divided into the early and late changes.

Early changes. (1) All three charts show early depression of both lymphocytic and polymorphonuclear counts. In two of the three cases the lymphocytes show the drop earlier than the polymorphonuclears; in the third case the drop in both is simultaneous. The time when these phenomena appear is not constant, the lymphocytes showing a drop at two weeks in two cases and at four weeks in the third case. In the third case, however, it is not possible to say that the drop did not appear earlier, inasmuch as no count was taken until three weeks after the first treatment.

In the same way, the polymorphonuclears show the drop at two, four, and six weeks repectively in the three charts.

(2) One case (III) shows a recovery of the lymphocytes at the sixth week, another (VI) at two months. The third case (IV) shows no such reaction up till the last count (at six weeks). It is interesting to note in this connection that case III lived nine months after treatment was begun.

In case VI the lymphocytic recovery is accompanied by a sharp reaction in the polymorphonuclear series, for, although the absolute lymphocyte count rises to a point above normal, the total white count also rises and the relative lymphocyte count remains about as before. This patient died four months after treatment was begun. Case IV shows at six weeks a beginning leucocytosis and a further depression of the lymphocytes, changes which point to impending death. The patient died four months after treatment was begun.

Late changes. (1) The most noteworthy late change is the terminal leucocytosis. In case VI this is found to be very marked and is characterised by enormous increase in the absolute polymorphonuclear count together with moderate decrease in the absolute lymphocyte count, factors which combine to give a very low relative lymphocyte count and correspondingly high relative polymorphonuclear count.

(2) Before the leucocytosis sets in another change may be noted. This is the change in relative counts from two and one-half to three months after the institution of treatment, the lymphocytes decreasing, the polymorphonuclears increasing. This apparently is the signal for the collapse of the patient's resistance and presages the terminal stage.

It may now be asked with reason: How big a part does the radium play in causing these changes, and how far are they due to the disease process? In answer it would seem fair to claim that the radium is responsible for the early changes, that is, the fall in lymphocytes and polymorphonuclears; but that the later changes, i.e., the marked change in relative counts and the terminal leucocytosis, represent the breakdown of the body's resistance and its final effort to combat the flood of

toxic products circulating in the blood stream. In this sense, the lymphocyte may be said perhaps to act as a rough indicator of the bodily resistance toward the later stages of the disease before the terminal leucocytosis has set in. Its practical value in this connection, however, is small, because it does not show any characteristic change until the break-down of the patient is clinically all too obvious.

Tables Showing Remoter Blood-Changes Following Combined x-ray and Radium Treatments

Group 2

CASE I	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment...............					
2½ months after...............	9,500[1]	5,900[1]	2,450[1]	62[1]	26[1]
5 months after...............	7,500	4,850	1,350	65	18
6 months after...............	7,400	3,750	2,200	51	30
Several short treatments: Heavy treatment begun just before next count					
11 months after...............	6,200[1]	4,850[1]	875[1]	78[1]	14[1]
12 months after...............	13,500	11,350	1,200	84	9
12½ months after...............	14,500	12,200	1,450	84	10

Case I. (1) The total white count shows a steady drop, lasting until the eleventh month, followed by a marked rise from the twelfth to thirteenth months.

(2) The lymphocytes show a sharp drop between two and one-half and five months, followed by a compensatory rise at the sixth month, while the polymorphonuclears show only an absolute decrease after the first five months, the relative decrease appearing first at six months, at which period it is overshadowed by the lymphocytic increase.

(3) The lymphocytes show a marked drop at the eleventh month which accounts for the greater part of the drop in total white count. The percentage of polymorphonuclears correspondingly makes a great jump, although the absolute number shows only a slight increase.

(4) At the twelfth month there is a sharp increase in total white count and polymorphonuclear count, which explains the increase in polymorphonuclear percentage and the decrease in lymphocyte percentage.

To summarise, this chart shows at five months a primary decrease in lymphocytes, followed by a temporary compensatory rise (at six months) and, finally by a gradual relative decline. The corresponding fluctuation in the total white count is determined largely by the lymphocytic changes until the twelfth month, when there appears a polymorphonuclear leucocytosis. This final change is presaged as in case VI at eleven months by a change in relative counts without any increase in total white count.

CASE II	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment.............					
5 months after...............	16,500[1]	13,350[1]	1,650[1]	81[1]	10[1]
Heavy treatment instituted one week later					
6 months after................	19,000	15,600	2,300	82	12
7 months after................	18,000	15,500	1,800	86	10
8 months after................	21,000	18,500	1,700	88	8
9 months after (approximate time of death)...............	44,000	41,350	1,750	94	4

Case II. This chart shows: (1) A steady increase in total white count.

(2) A gradual increase in percentage of polymorphonuclears.

(3) A gradual decrease in percentage of lymphocytes except for one period (six months) when there is a slight temporary rise, accompanied by a rise in actual numbers. This represents a transitory stimulation following the first trial of a thirty-hour treatment. In this chart, again, the terminal leucocytosis is foreshadowed by the changing percentage counts. This change is due to a steady increase in the absolute polymorphonuclear count, the absolute lymphocyte count remaining practically stationary throughout.

CASE V	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	12,000	8,750	2,150	73	18
4 weeks after	9,000	7,000	1,250	78	14
15 weeks after	5,500[1]	4,100[1]	800[1]	75[1]	14[1]
19 weeks after	12,500[1]	10,000[1]	2,000[1]	80[1]	16[1]
22 weeks after	15,500	14,400	950	93	6
27 weeks after	Died				

Case V. The chart of this case shows: (1) A fall in total white count continuing until fifteen weeks after treatment was instituted, after which time the terminal rise begins.

(2) The lymphocytes show a primary drop after four weeks which is proportionally greater than the rise of polymorphonuclears. At fifteen weeks the polymorphonuclears show a more distinct drop than the lymphocytes.

(3) At nineteen weeks both groups of white cells show an approximately proportional rise, while at twenty-two weeks the polymorphonuclears show a rise, though this is not so marked as the drop in lymphocytes. This is a beginning terminal leucocytosis. If later counts had been made the polymorphonuclears would probably have shown a large relative increase.

Summary. This chart shows a primary lymphocytic drop followed by a drop in polymorphonuclears, the former starting at four weeks, the latter at eighteen weeks. The relative counts show an almost steady increase of polymorphonuclear cells and an almost steady decrease of lymphocytes. The terminal leucocytosis is preceded as usual by a definite though gradual change in the relative proportion of polymorphonuclears and lymphocytes.

Case VIII. This chart shows: (1) Irregular fluctuation of total white count and of total polymorphonuclear count.

(2) Depression of lymphocytic series from the second to the third week, as evidenced by a primary drop in total lymphocyte count despite an increase in total white count, and by the decrease in relative count at the third week in spite of the drop in total white count at that time.

CASE VIII*	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	8,600[1]	6,500[1]	1,550[1]	76[1]	18[1]
2 weeks after	12,100[1]	10,400[1]	1,330[1]	86[1]	11[1]
3 weeks after	7,200	6,400	575	89	8
4 weeks after	11,000	9,450	1,320	86	12
5½ weeks after	9,100	7,450	1,080	82	12
6½ weeks after	11,000[1]	8,250[1]	2,100[1]	75[1]	19[1]
7 weeks after	8,500	7,500	510	88	6
9½ weeks after	Dead				

* This patient was given radium treatments at an earlier date [August 1915] in a different institution. Dosage and filtration at that time were not recorded.

(3) A readjustment of relative counts from the fourth to sixth weeks.

(4) A sharp drop in absolute and relative lymphocyte count at the seventh week without any leucocytosis, presaging the death of the patient two and one-half weeks later.

Summary. This case shows an initial depression of the lymphocytes followed by temporary recovery, and a final sharp drop shortly before death. The polymorphonuclears show no definite changes.

CASE IX	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	8,400	5,600	1,850	67	22
1 month after	6,500	5,000	1,000	77	16
2 months after	13,000	10,300	1,700	79	13
3 months after	14,000[1]	11,350[1]	2,100[1]	81[1]	15[1]
4 months after	15,500	14,700	450	95	3
Last count, 4 months, 9 days	19,300	17,500	1,150	91	6
4 months, 10 days	Death				

Case IX. This chart shows the following:

(1) A preliminary drop in total white count, followed by a steady slight rise and slight terminal leucocytosis.

(2) A sharp drop in lymphocytes, absolute and relative, accounting for most of the preliminary drop in total white count.

(3) A steady increase in polymorphonuclear count, absolute

and relative, with corresponding decrease in lymphocytes, most marked in the relative counts.

Summary. This chart shows a marked fall in lymphocytes one month after treatment was begun, accompanied by a slight decrease in polymorphonuclear count. This is followed by a steady increase in polymorphonuclear count and an irregular lymphocytic curve. The lymphocytes do not show a further marked drop until a short time before death. The last count, taken the day before death, shows a final effort to rally on the part of the lymphocytes. The usual terminal leucocytosis is seen.

CASE X	TOTAL WHITE BLOOD CELLS	TOTAL POLY-MORPHO-NUCLEARS	TOTAL LYMPHO-CYTES	PER CENT POLY-MORPHO-NUCLEARS	PER CENT LYMPHO-CYTES
Before treatment	14,000	10,800	2,250	77	16
2 weeks after	9,000	7,000	1,500	78	17
3 weeks after	9,500	6,650	2,350	70	25
4 weeks after	8,000	5,600	2,000	70	25
5 weeks after	6,500	4,200	1,800	65	28
6 weeks after	7,500	4,850	2,300	65	31
Last count $6\frac{1}{2}$ weeks, 3 days before death	13,000[1]	9,100[1]	3,250[1]	70[1]	25[1]

Case X. This chart shows a decrease in total white count from the initiation of treatment until a week before death, followed by a terminal rise. The lymphocytes show a primary drop in absolute count after the first two weeks but a steady rise in percentage count, reaching its maximum a week before death. Even after the terminal leucocytosis appears the lymphocytes maintain a high percentage, although most of the increase is in the polymorphonuclears.

Group 2

From such a mass of detailed observations it is hard to deduce any broad principle. For the sake of simplicity the remote results will again be divided into the early and late blood-changes.

Early changes. These can be studied in cases V, VIII, IX, and X.

(1) There is first to be noted, as in group 1, a primary lymphocytic drop in all cases. This is usually both absolute and relative, although in one case (X) the relative figure shows almost no change. This case is atypical in other ways, as will be seen later.

(2) Three out of the four cases (V, IX, and X) also show a fall in the absolute polymorphonuclear count, though in only one case is the fall relatively as great as the fall of lymphocytes (case X). In one case (VIII) there is no fall in the absolute polymorphonuclear count. In other words the action on the lymphocytic system is more constant and profound than the action on the polymorphonuclears.

(3) All cases show some tendency on the part of the lymphocytes to attempt a recovery; case V at nineteen weeks, case VIII at four and six and one-half weeks, case IX at three months, and case X from three to six weeks.

(4) The time at which these changes take place is not constant. The lymphocytic fall occurs at from two to four weeks and may be maintained in some degree until the end of the second month. The attempt at recovery, however, may occur at any period thereafter, from three weeks to nineteen weeks.

Late changes. (1) Terminal leucocytosis. This was found to be present in five out of six cases. The sixth case (VIII) died while no longer under observation and no autopsy was performed. It did not seem probable at the time when she left the hospital that she would die for some months, whereas she actually died two and one-half weeks later. The possibility of some intercurrent condition must be considered here, and it must also be borne in mind that she may have developed a leucocytosis after leaving the hospital.

(2) The terminal leucocytosis is due primarily to an increase in polymorphonuclears, although there is often an absolute as well as relative decrease in lymphocytes at the same time.

(3) Almost all the cases showed a tendency towards relative increase of polymorphonuclears and relative decrease of lymphocytes before the terminal leucocytosis appeared.

(4) The one case which showed no leucocytosis upon dis-

charge (case VIII), that is to say two and one-half weeks before death, did show a great decrease in absolute and relative lymphocyte counts just prior to this date, a condition which has been shown to precede this terminal leucocytosis.

(5) One case (X) showed a steady relative increase in lymphocytes from two weeks until six and one-half weeks, three days before she died. This, however, was not accompanied by an absolute increase until the terminal leucocytosis appeared. In other words, the relative increase was really due to a decrease in polymorphonuclears, in which connection it is interesting to note that the smears showed myelocytes and nucleated red cells, in spite of falling white count, indicating an exhausted bone-marrow which was endeavoring to its utmost to compensate for its loss of normal function.

From a glance at these findings it will readily be seen that the essential effects of radium treatment are the same, whether it be given in conjunction with *x*-ray or not. Thus in both groups of cases the early depressing effect on the lymphocytes, and to a less marked degree on the polymorphonuclears, is found; in both groups, also, there is a tendency to lymphocytic regeneration after varying periods in those cases whose resistance has not altogether broken down. In both groups we find a change in relative counts toward the end, the polymorphonuclears increasing, the lymphocytes decreasing; and, finally, in both groups there is almost invariably a terminal leucocytosis, due primarily to absolute increase in polymorphonuclears, but usually accompanied by some decrease in absolute lymphocyte count. It seems reasonable, therefore, to disregard the scattered *x*-ray treatments as factors in determining the blood-changes here noted.

GENERAL SUMMARY AND CONCLUSIONS

1. The blood of ten cases of squamous-cell carcinoma of the cervix uteri and vagina has been studied, in order to ascertain the immediate and remote effects of radium and *x*-ray treatments upon the formed elements of the blood.

2. The immediate effects of radium on the blood are not

altered qualitatively by previous x-ray or radium treatments, although the quantitative action may be somewhat diminished during a second treatment.

3. The remote effects of radium on the blood are essentially similar to the effects of combined x-ray and radium treatment.

4. Individual slight differences in response to radium applications are often noted to occur again on a second application in the same individual.

5. The immediate effects of radium on the blood are the following:

a. An immediate drop in total white count reaching its maximum from one-half to six hours after the application.

b. A return of the total white count to its former level within twenty-four hours after the application, usually within the first twelve hours.

c. An occasional secondary rise of the total white count to a point well above its original level from twelve hours to three days after the application.

d. A close adherence of the total polymorphonuclear count to the curve of the total white count.

e. An absence of characteristic changes in the total lymphocyte and total large mononuclear counts.

f. A tendency of the total lymphocyte count to follow in some degree the fluctuations of the total white count, especially when these are marked. This effect is not constant.

g. A tendency of the relative lymphocyte count to drop, and of the polymorphonuclears to rise during the course of treatment. This tendency is reversed during the period immediately following the removal of the radium.

6. Remote effects of radium treatment on the blood are as follows:

a. Early.

(1) Fall in lymphocyte count from two to four weeks after treatment, sometimes lasting till the end of the second month.

(2) Fall in polymorphonuclears after treatment, sometimes simultaneous with the fall in lymphocytes but usually coming later and being less striking.

(3) An attempt of the lymphocytes to recuperate, as shown by a rise in most cases at some later date, varying from three to nineteen weeks after treatment, to the approximate level seen before treatment.

b. Late.

(1) Change in the relative counts as the patient's resistance weakens, with increase in polymorphonuclears and decrease of lymphocytes, but without leucocytosis.

(2) Terminal leucocytosis, due in the main to increase of the absolute polymorphonuclear count, although usually accompanied by an absolute decrease in lymphocytes.

THEORETICAL CONSIDERATIONS

In conclusion, it may not be amiss to speculate briefly upon some points brought out in the above study.

1. In the first place, what do these figures show us to prove or disprove the theory that the lymphocyte is the essential factor in immunity or resistance to tumors? It seems fairly clear from the above that in the terminal stages of death from cancer there is a relative and often an absolute lymphopenia. It is, however, also true that this lymphopenia may not appear until a few days before death (case X); in fact, there may be a slight excess of lymphocytes as late as this. It would hardly seem reasonable, therefore, to assume that the lymphocyte is an infallible index of the patient's state of resistance at any given period, seeing that the patient in question (case X) was just as surely moribund one week before death, when she had 31 per cent lymphocytes and a total lymphocyte count of 2300, as she was four days later when the percentage had dropped to 25. It would then be useless to attempt to estimate a patient's resistance at any given time by referring to the absolute and relative lymphocyte count. On the other hand, if the blood has been systematically followed over a long period, it is possible to predict a fatal ending by the changing relative counts of lymphocytes and polymorphonuclears, the former decreasing, the latter increasing, though the practical value of this fact is very small, inasmuch

as the same conclusion may be reached at an earlier date by clinical observation.

2. Can these changes in the blood be used as a guide to the proper intervals and dosage of radium? This question can not be answered on the basis of the above figures, inasmuch as all the patients were so far advanced in the disease as to be beyond the hope of cure, at least with the small amount of radium which we had at our command.

Seeing, however, that the first sign of the final collapse is given by a fall in relative lymphocyte count, it does not seem unreasonable to suggest that no second radium treatment should be given until the lymphocyte count has recovered from the preliminary depression consequent to the first application. It would be interesting to know the behavior of the blood in patients treated under more favorable circumstances, that is to say, with larger doses and few applications.

3. Do these figures indicate anything of importance in regard to the mode of action of radium? It is certainly striking that the response of the hematopoietic organs to the application of so small an amount should be so immediate and yet so lasting. If we are to accept the theory that the beneficial effects of radium are dependent solely upon its local action, it must first be proved that these profound blood-changes are not incompatible with complete and lasting cure. In one instance we have known of a case which had been treated with heavy dosage of radium coming to autopsy without showing any demonstrable remains of carcinoma or any morbid process that could explain death. No studies of the blood or blood-forming organs were made. Is it not conceivable that in this case, although the carcinoma was locally cured, the patient was killed by the radium? The authors have been particularly interested in the close analogy between the immediate blood changes following radium treatment, as noted above, and those mentioned by Jobling (11) and Scully (12) as occurring after the intravenous injection of foreign protein in the treatment of arthritis and other conditions. Similar observations have been made by our colleague, Dr. B. F. Schreiner (13), following injections of

phylacogen. It is not impossible that the early blood-changes following radium application are due to the sudden introduction of protein substances, the products of cell destruction, into the blood stream, with the same effects on the blood-forming organs as are brought about by the intravenous injection of foreign protein. Even if this be the case, however, we are not justified in assuming that the therapeutic effect of radium is dependent on the formation of these products of abnormal cell destruction. It should be emphasized, in closing, that, while we have abundant evidence, both clinical and histological, that radium has a definite local action on malignant growths and that this action is detrimental to their development, there is also evidence of a more general effect whose nature we do not by any means understand. It is to be hoped that further blood-studies from the physicochemical as well as from the morphological standpoint will clear up this obscurity, and will enable us to explain some of the miraculous cures and unexpected disappointments which we encounter when employing radium as a therapeutic agent.

Finally, we wish to express our indebtedness to Dr. H. R. Gaylord, Director of the Institute, for valuable suggestions at the outset of the work, and to Miss Alice Thornton for her careful attention to the details of the routine counts and charts

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PROTOCOLS OF PATIENTS WITH CHARTS ILLUSTRATING IMMEDIATE AND REMOTE EFFECTS OF RADIUM APPLICATIONS

Case I. L. S. Married. Age 48. Metrorrhagia, June, 1915. Percy cautery operation, July, 1915. Hemorrhage (approximately 500 cc.) three weeks later. Entered hospital June, 1915. Ulcerated immobile cervix. Died November, 1916. Multiple subcutaneous metastases. Fifteen radium applications; sixteen x-ray treatments. (See chart 20.)

Case II. M. P. Single. Age 30. Bloody vaginal discharge, December, 1914. Hysterectomy, January, 1915. Gained 30 pounds, but bladder very irritable. Bleeding recurred February, 1916. Entered hospital at this time. Nodular immovable mass in vault of vagina. Urinary incontinence, August, 1916. Sciatica, October, 1916. Died, November, 1916. Metastases in retroperitoneal lymph nodes; invasion of bladder and sciatic nerve. Eight radium and eleven x-ray treatments. (See chart 21.)

Case III. M. K. Married. Age 30. Menorrhagia, 1912–15, increasing and later developing into continuous bleeding. Curettage, August, 1915. Hysterectomy, September, 1915. Discharge and bleeding, March, 1916. Entered hospital at this time. Immovable, indurated, ulcerated mass in vaginal vault. Foul watery discharge. Rectovaginal fistula, August, 1916. Died, December, 1916. No autopsy. Three radium treatments. (See chart 22.)

Case IV. M. H. Married. Age 40. Bloody vaginal discharge, November, 1915. Hemorrhage, March, 1916. Cautery applied. Entered hospital, April, 1916. Large ulcerated, hard tumor involving cervix and left broad ligament. Cervix immovable. Hemorrhage, July, 1916. Uraemia and death, August, 1916. Metastases in lungs; chronic nephritis. Two radium treatments. (See chart 23.)

Case V. E. W. Married. Age 50. Menorrhagia, 1913. Curettage. Bleeding returned three months later. Sudden anuria, April, 1916. Cystotomy, August, 1916. Admitted to hospital two weeks later. Extensive induration along anterior vaginal wall and cervix. Urinary flow returned after first radium treatment. Metastatic lymph nodes in groin removed, December, 1916. Uraemia and death, February, 1917. Metastases in retroperitoneal lymph nodes, liver, and lungs; invasion of bladder and rectum. Double hydronephrosis. Seven radium and seven x-ray treatments. (See chart 24.)

Case VI. M. W. Widow. Age 56. Hemorrhages, June, 1916 and

August, 1916. Admitted, September, 1916. Large spongy mass springing from cervix and invading right broad ligament. Marked secondary anaemia. Gradual loss of strength. Died, January, 1917. Metastases in peritoneum and lung; invasion of bladder; chronic nephritis. Five radium treatments. (See chart 25.)

Case VII. P. S. Married. Age 42. Mass in uterus, 1912. Specimen removed; said not to be cancer. Bleeding by vagina, 1914. Panhysterectomy, 1914. Watery discharge for past two weeks. Admitted to hospital, September, 1916. Ulcerating nodular mass in vault of vagina. Bloody discharge. Vesico-vaginal fistula, November, 1916. Has not reported since. Three radium treatments. (See chart 26.)

Case VIII. J. F. Married. Age 59. Polyp removed from cervix, June, 1915. Cautery applied, August, 1915. Bloody vaginal discharge continued. Radium treatment for supposed fibroids, September, 1915. Severe external and internal burns resulted. Vaginal discharge continued, often bloody. Nodules recently discovered in vaginal wall by physician. Severe pain in lower abdomen. Admitted to hospital, October, 1916. Uterus enlarged. Many small nodules in vaginal wall. Tenderness beneath scar of old burn in right lower quadrant. Small metastases in both groins. Gradual loss of weight. Discharged December, 1916. Died one week later. No autopsy. Three radium and one x-ray treatment. (See chart 27.)

Case IX. C. M. Widow. Age 50. Painful urination, spring of 1916. Occasional hemorrhages since July, 1916. Watery vaginal discharge for past six weeks. Admitted to hospital, November, 1916. Extensive nodular induration of entire vaginal wall. Exquisite tenderness, making examination almost impossible. Temporary local improvement, followed by rapid loss of weight and strength. Died, March, 1917. Autopsy: Extensive metastases in reproperitoneal lymph nodes, lungs, and liver; invasion of bladder. Two radium and four x-ray treatments. (See chart 28.)

Case X. B. C. Married. Age 43. Menorrhagia, 1913. Curettage. Diagnosis of cancer made. Panhysterectomy, March, 1914. Well until three months ago. Since then severe pains in hips, back, and shoulders. Bed-ridden. Small ulcer in vaginal vault. Large masses in both iliac fossae. Severe sweats. Oliguria. Loss of pain under treatment and decrease in size of masses. Gradual loss of weight and strength; death in uraemia, January, 1917. Autopsy: chronic nephritis; bronchopneumonia; metastases in retroperitoneal

lymph nodes, lungs, and liver; meningitis. Local lesion almost destroyed. (See chart 29.)

Case XI (*control*). L. Z. Married. Age 35. Vaginal discharge, sometimes bloody, since March, 1916. Hemorrhage, March, 1917, followed by slight continuous bleeding. Admitted to hospital, May, 1917. Examination showed extensive ulcerated, nodular mass, involving cervix and broad ligaments. Considerable local and general improvement under treatment. Two radium treatments. Patient still in the hospital. (See chart 30.)

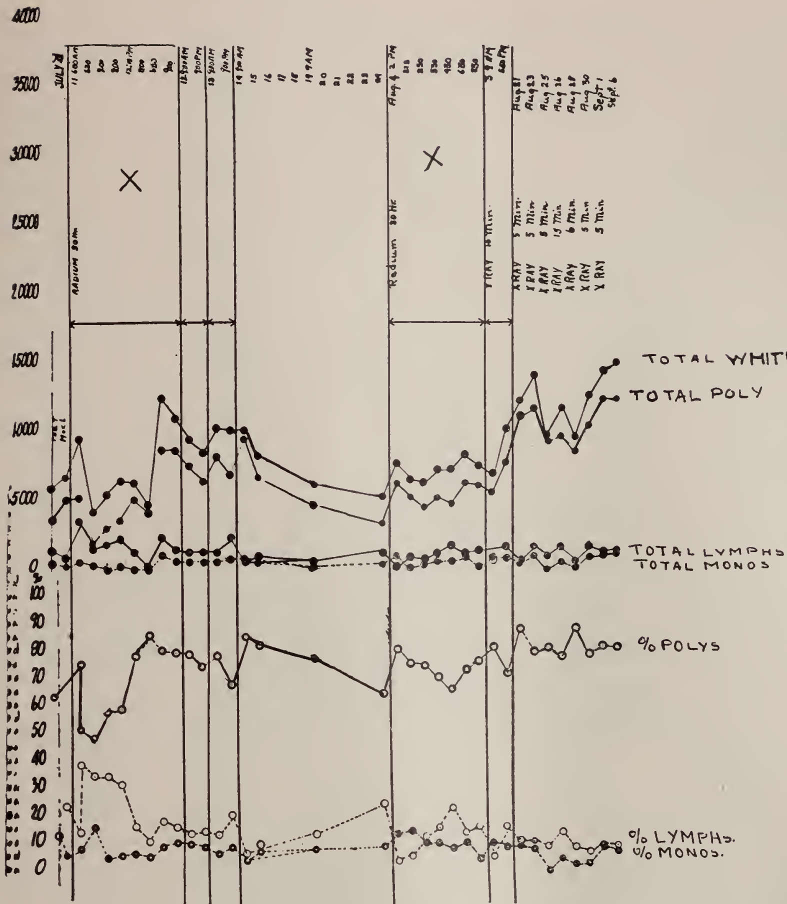

Chart 20

Days on which more than one count was made are designated by cross-lines with arrow-points at either end. The heavy vertical lines at either end of the cross-lines represent the beginning and end of the day in question. Except where marked by these cross-lines only one count was made on any given day. Days chosen for studying the immediate blood changes are marked thus: x.

1. Primary drop in lymphocytes, followed by temporary recovery, and final relative decline.

2. Diminished response to second radium treatment.

3. Terminal leucocytosis.

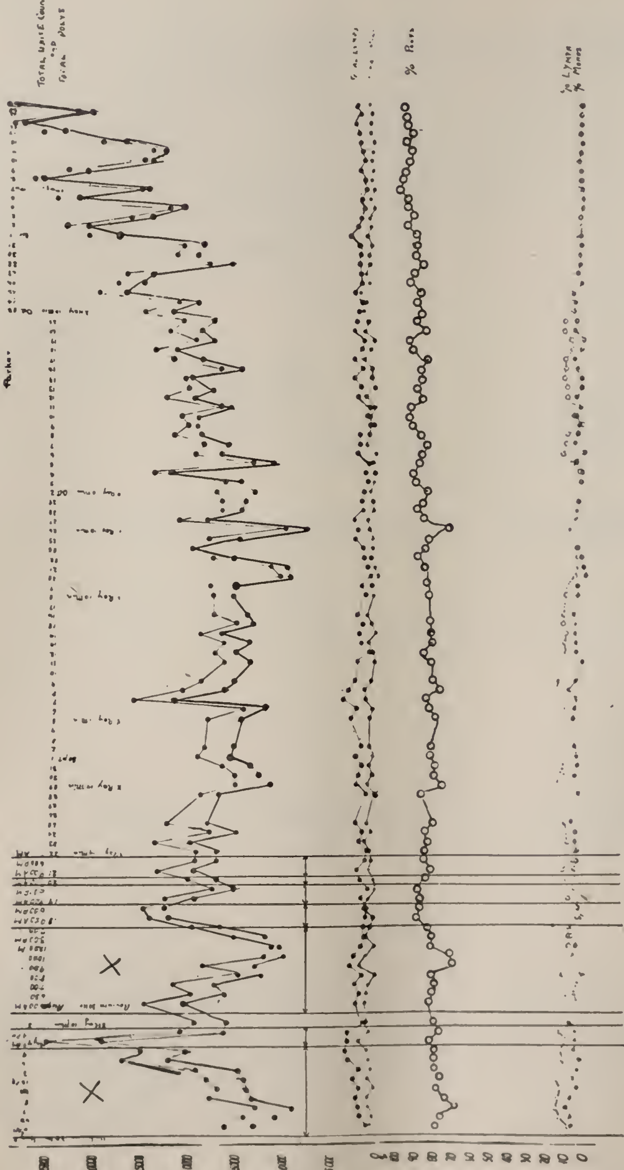

CHART 21

For explanation of vertical and cross-lines see under case 1.

1. Steady decline in total lymphocyte count.
2. Terminal leucocytosis, preceded by decrease in relative lymphocyte count and increase in relative polymorphonuclear count.
3. Typical immediate blood-changes following radium application, somewhat modified on second application.

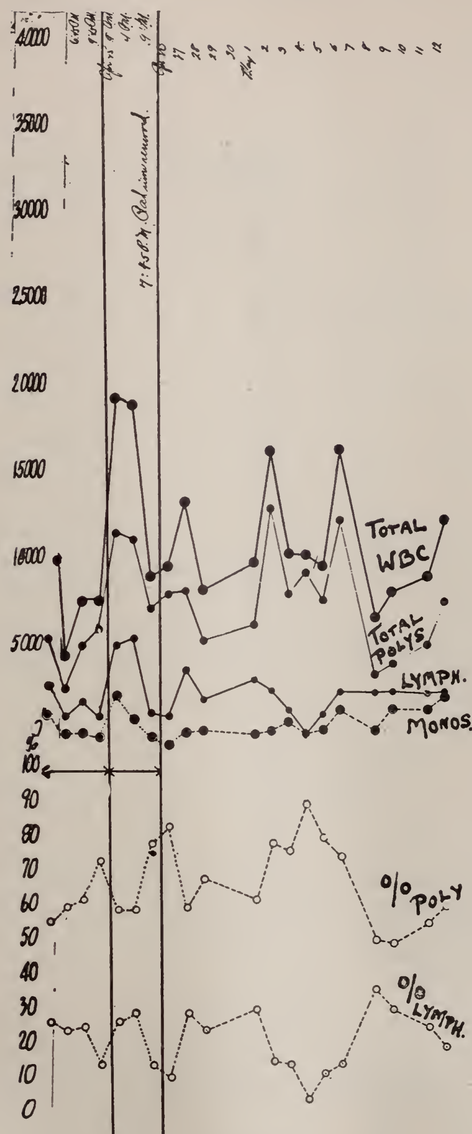

CHART 22

For explanation of vertical and cross-lines see under case 1.

1. Typical early reaction, with immediate drop of white count, followed by secondary rise.

2. Primary drop in lymphocytes reaching lowest point at end of fifth week, followed by recovery.

3. Slight depression of polymorphonuclear series at end of sixth week.

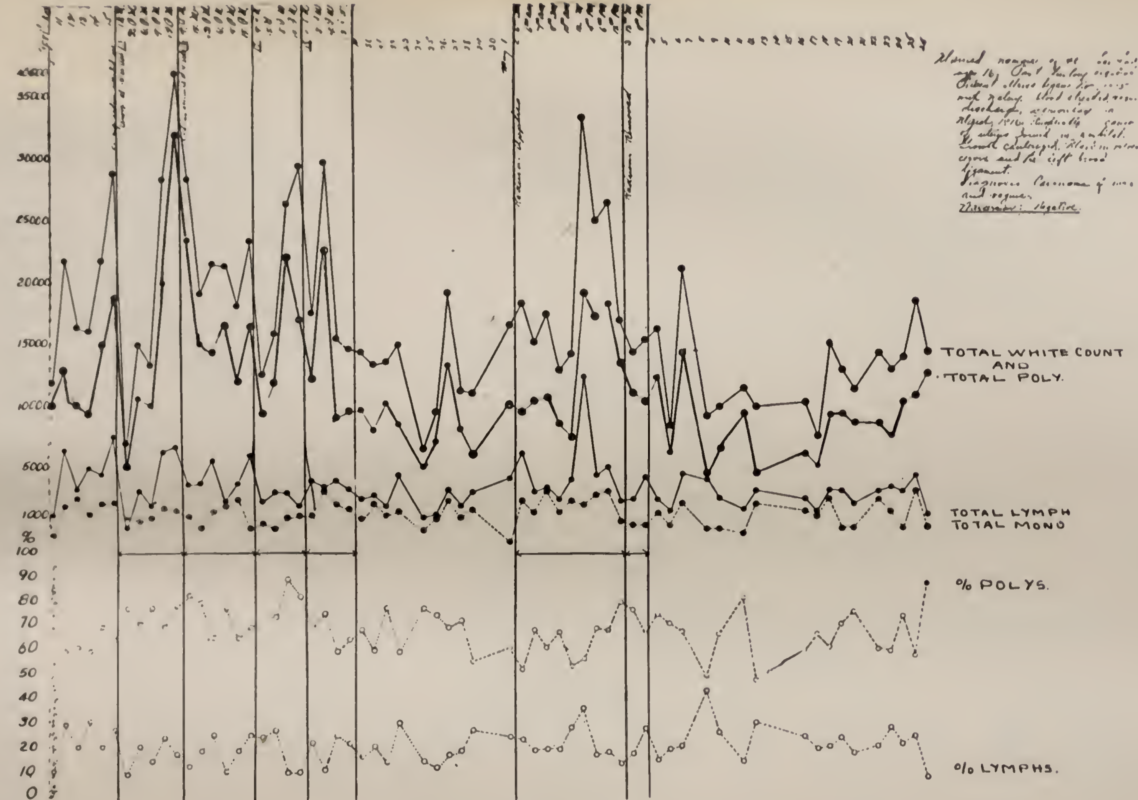

CHART 23

For explanation of vertical and cross-lines see under case 1.

1. Typical immediate drop in white cells after two successive radium applications, followed in both instances by a secondary rise. The reaction is slightly less pronounced on the second of the two applications.

2. Steady drop in total polymorphonuclear count until the beginning of the terminal leucocytosis.

3. Beginning terminal leucocytosis, preceded by drop in relative lymphocyte count and corresponding rise in relative polymorphonuclear count. (The chart was not continued long enough to show the full development of the terminal leucocytosis.)

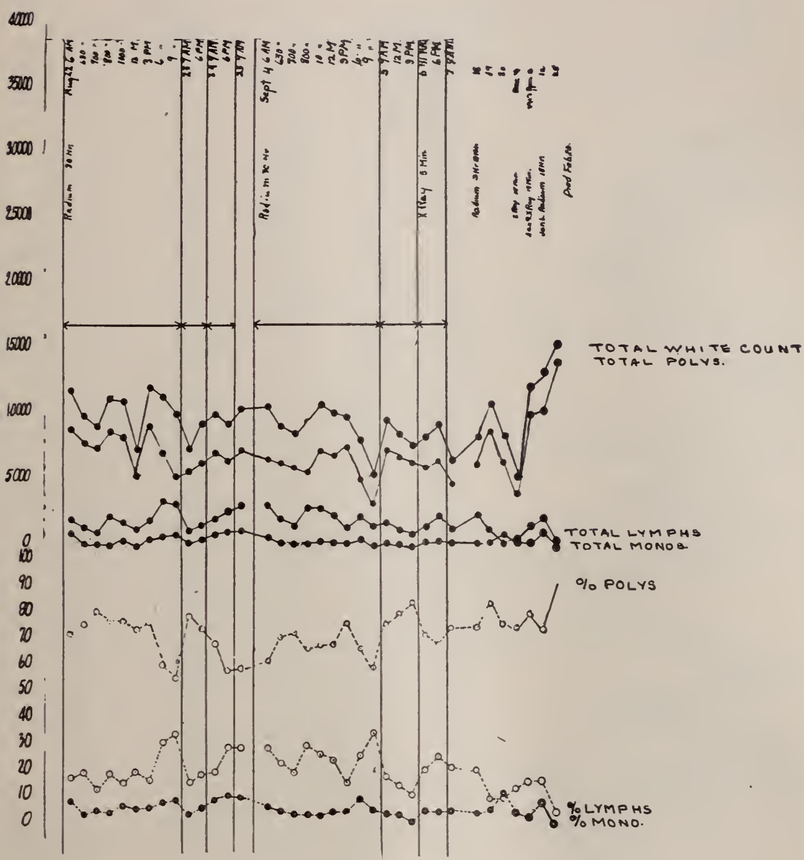

CHART 24

For explanation of vertical and cross-lines see under case 1.

1. Atypical early change in white count: repeated on later application.

2. Decrease of all white cells, but especially of the lymphocytes, with rise of polymorphonuclear percentage.

3. Terminal leucocytosis and lymphopoenia.

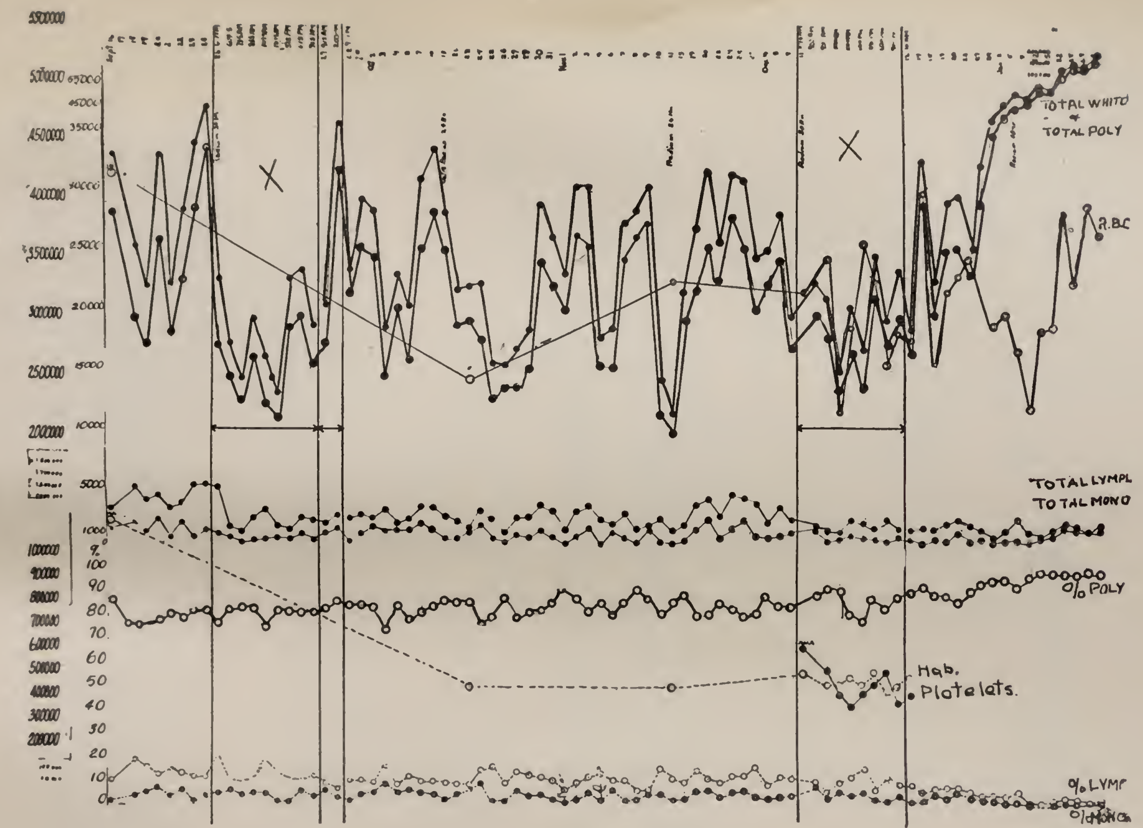

CHART 25

For explanation of vertical and cross-lines see under case 1.

1. Characteristic reaction in white cells immediately after radium application, less pronounced the second time than the first.
2. Tendency of total lymphocytes to fall from the time of the first application.
3. Irregular curve of total polymorphonuclears, with tendency to fall.
4. Marked terminal polymorphonuclear leucocytosis, with consequent drop in relative lymphocyte value.
5. Immediate drop in platelet and red cell counts, followed in the case of the red cells by a compensa-

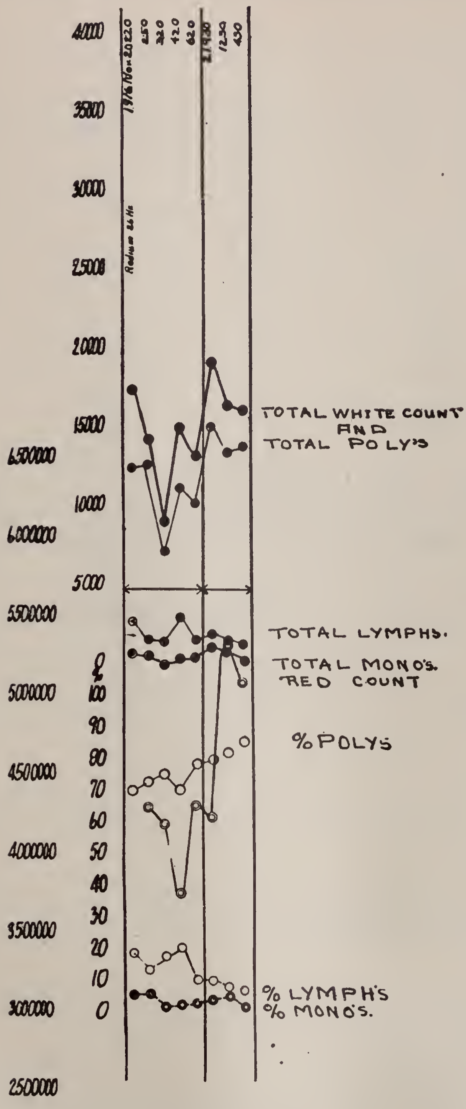

CHART 26

For explanation of vertical and cross-lines see under case 1.

1. Characteristic primary drop in white count.

2. Change in percentage values of lymphocytes and polymorphonuclear cells during treatment.

3. Drop in red cell count, followed by marked rise.

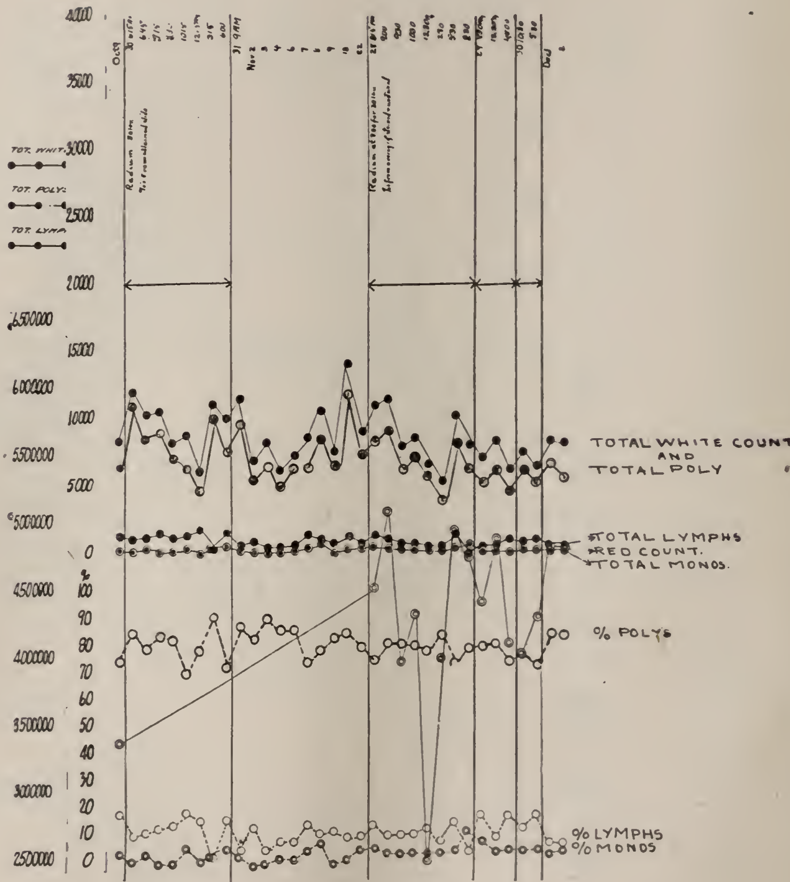

CHART 27

For explanation of vertical and cross-lines see under case 1.

1. Characteristic immediate drop in white count.
2. Absence of secondary rise.
3. Preliminary slight drop in lymphocytes, followed by recovery.
4. Fall in lymphocytes just before discharge, both in total numbers and percentage value, indicating near approach of terminal leucocytosis. The patient left the hospital before any leucocytosis developed, but died less than three weeks later.

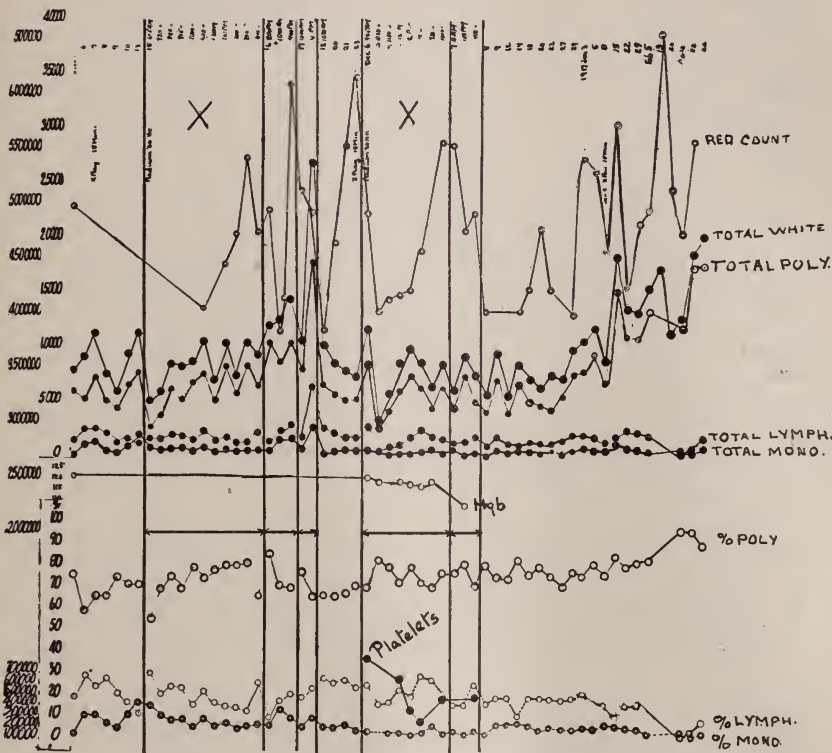

CHART 28

For explanation of vertical and cross-lines see under case 1.

1. Absence of secondary rise of white count after radium application. The usual primary drop is seen.

2. Tendency for slight decrease in total and percentage counts of lymphocytes.

3. Tendency to slight drop in total polymorphonuclear count, followed by terminal leucocytosis.

4. Immediate drop in platelets during radium application.

5. Drop in red count during early part of radium treatments, followed by an early secondary rise, and later by a second drop.

6. The red cells show a terminal rise, synchronous with the terminal leucocytosis.

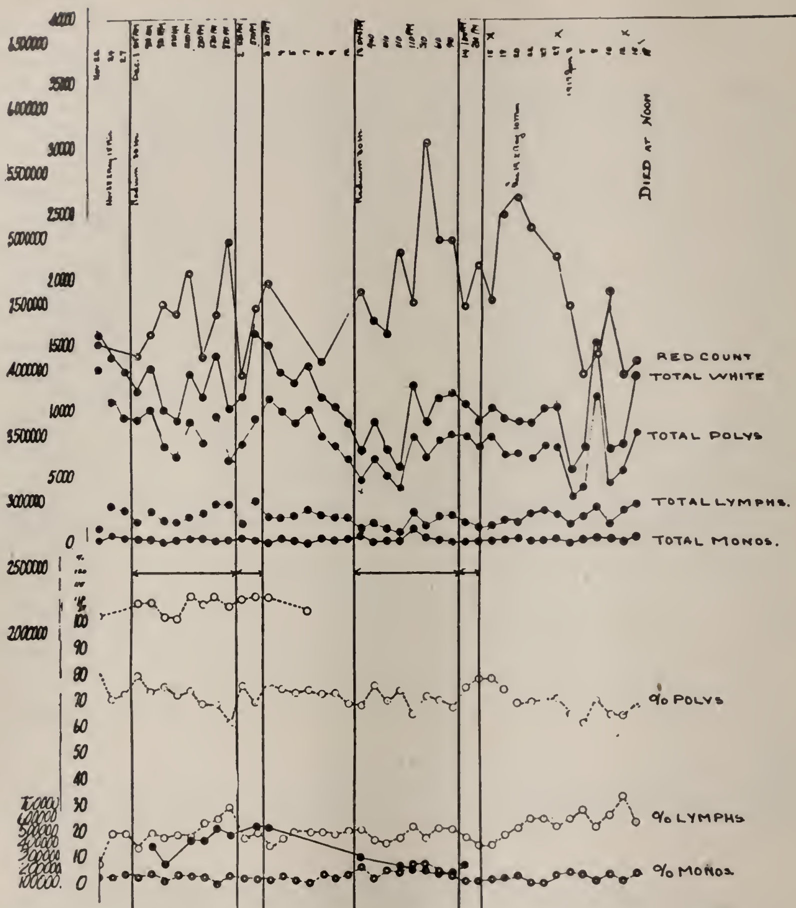

CHART 29

For explanation of vertical and cross-lines see under case 1.

1. Atypical immediate changes in white count: the same preliminary rise noted in subsequent treatment.

2. Steady drop in polymorphonuclears until just before the terminal leucocytosis appears.

3. Preliminary slight drop in total lymphocytes, corresponding to the drop in polymorphonuclears; this is followed by a steady rise until a few days before death. The rise in lymphocytes accounts for part of the slight terminal leucocytosis.

4. Rise of red count during each application, followed by return to a point below the former level.

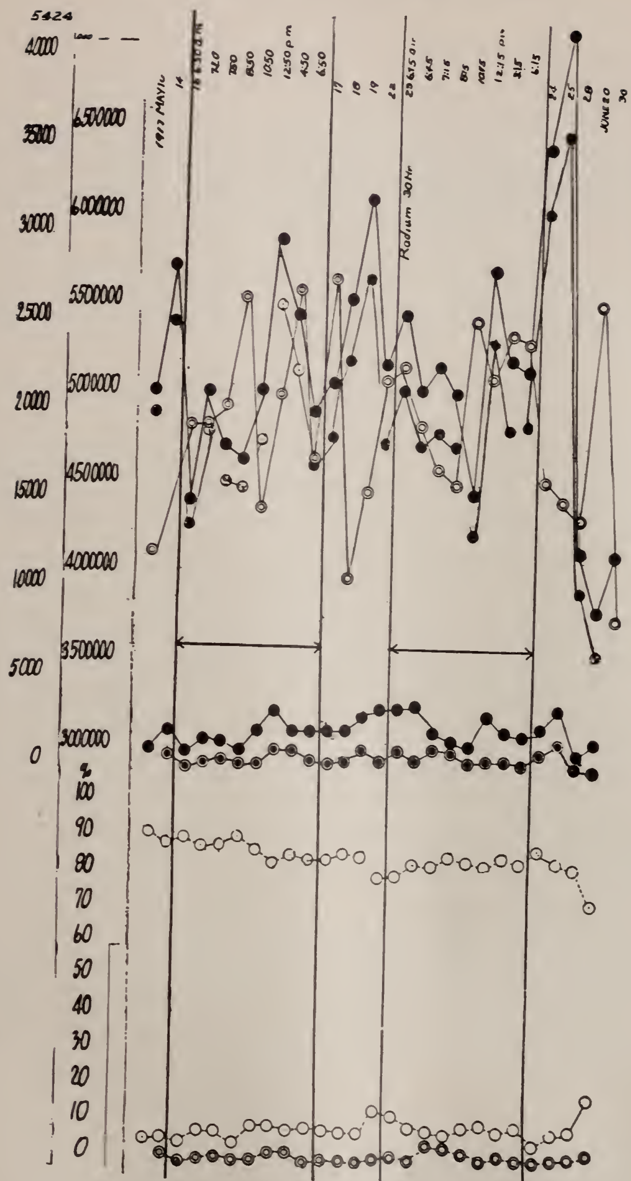

CHART 30

For explanation of vertical and cross-lines see under case 1.

1. Absence of preliminary drop in white count during control period; marked drop during treatment.

2. Absence of secondary rise in white count during control period; marked rise on second day after radium application.

THE INFLUENCE OF HEAT AND RADIUM UPON INDUCED IMMUNITY AGAINST TRANSPLANTED ANIMAL TUMORS

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From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director

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In several publications, Bashford (1) has called attention to the relationship existing between the growth energy of transplanted tumors and their power to induce the resistant state, and has also correlated the growth energy of these tumors with their resistance to the immunizing action of living cells. Broadly stated, his view point is: that the power to overcome the resistant state varies directly as the growth energy of the tumor, whether immunity result from the growth of the tumor itself (concomitant immunity) or be caused by normal living cells.

If Bashford's view be the correct one, then it should be possible to immunize against tumors which are refractory to the induced resistant state, and to increase the percentage of induced immunity against susceptible tumors, by depressing the growth energy of these neoplasms. This has, in fact, been done by Tsurumi, who (2) has demonstrated that certain sarcomata which are resistant to induced immunity can be rendered susceptible by exposing them to comparatively low degrees of heat for varying periods before inoculation. It should also be possible to bring out more distinctly the concomitant immunity produced by various growing tumors.

The growth energy of transplanted tumors can be depressed, also, by radium, as Wedd and Russ (3), and Wood and Prime (4), have shown. The retardation of growth energy was not a permanent alteration in the biology of the tumor, however, and persisted only for a few generations of transplants.

With these facts in mind, a series of observations upon the influence of radium and heat in induced immunity was undertaken with various tumor strains. The strains chosen were the Crocker Fund mouse sarcoma 180 and the Ehrlich mouse sarcoma, both refractory to the immunizing power of living cells, and the Jensen rat sarcoma, which is susceptible to the induced resistant state.

The technic used in depressing the growth energy of the tumors was as follows: 83 mgm. of radium element, screened by 0.4 mm. of brass and a thin glass cover-slip, were placed upon a strip of tumor 2 mm. thick, 2 to 3 mm. wide, and 20 mm. long, so that the screened radium capsule was superimposed upon the tumor material, strict aseptic precautions being observed. The exposure to radium was continued for thirty minutes.

When heat was used, strips of tumor of dimensions similar to those of the strips exposed to radium were placed in Ringer's solution in the incubator at 38°C. for two hours.

Portions of the tumor strain to be used in a given series were treated by radium or heat to depress their growth energy, according to the technic just described. Inoculations by needle of 0.003 gram[1] of the treated tumor were made into one group of animals immunized ten days previously with 0.05 cc. of spleen emulsion, and into another series of animals not immunized. These two series gave the percentage of induced and natural immunity with treated tumor. Another group of animals immunized ten days previously with spleen emulsion, in doses of 0.05 cc., were inoculated with 0.003 gram of the untreated tumor by needle. A final group of nonimmunized control animals was inoculated with similar doses of the untreated tumor at the same time. The last two groups inoculated with untreated tumor served to show the percentages of natural and induced immunity for the untreated neoplasm.

[1] In previous publications from the Imperial Cancer Research Fund and from this laboratory, the inoculation dose, when the needle method is used, has been estimated as 0.01 or 0.02 gram; but such grafts have recently been found, as a matter of fact, to weigh about 0.002 and 0.003 gram respectively.

In order to control the influence of the immunizing agent, the experiment was repeated with a fourth tumor strain, the English mouse carcinoma 199, a neoplasm which is moderately resistant to the immunizing power of living cells (Russell, (5)).[2] The technic and method used with this strain differed from that previously described only in that fetal skin emulsion was used instead of splenic pulp.

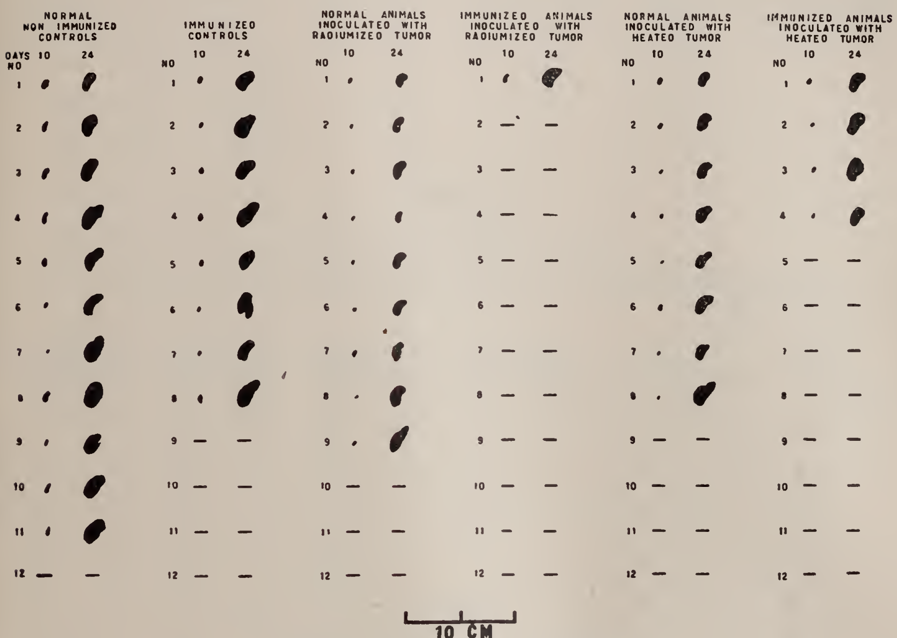

CHART 1. JENSEN RAT SARCOMA

Comparative influence of radium and heat previous to inoculation into immunized animals.

Charts 1, 2, 3, and 4 graphically portray our results in single unselected lots of 12 animals each, the entire material not being presented in chart form because of the large number of animals used.

Table 1, which gives the numerical data of each experiment,

[2] This laboratory is indebted for the tumor strain in question to Dr. J. A. Murray, Director of the Imperial Cancer Research Fund of London.

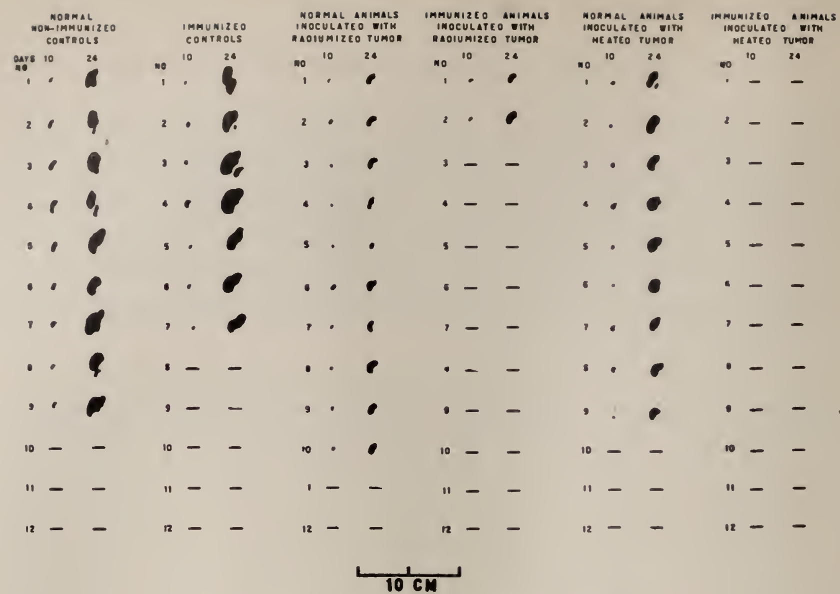

Chart 2. Mouse Carcinoma 199

Comparative influence of radium and heat previous to inoculation into immunized animals.

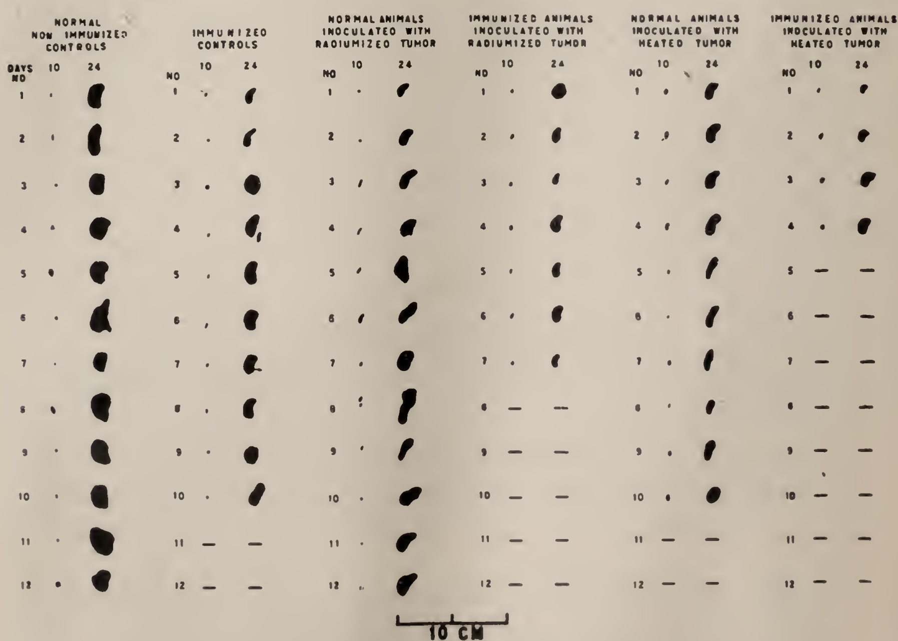

Chart 3. Mouse Sarcoma 180

Comparative influence of radium and heat previous to inoculation into immunized animals.

shows that depression of the growth energy of the four tumor strains chosen, whether caused by radium or heat, results in a marked increase in their susceptibility to the immunity produced by splenic pulp. The percentage of induced immunity against untreated tumor, as averaged for all four strains, was 29.25, while the groups immunized and inoculated with radiumized

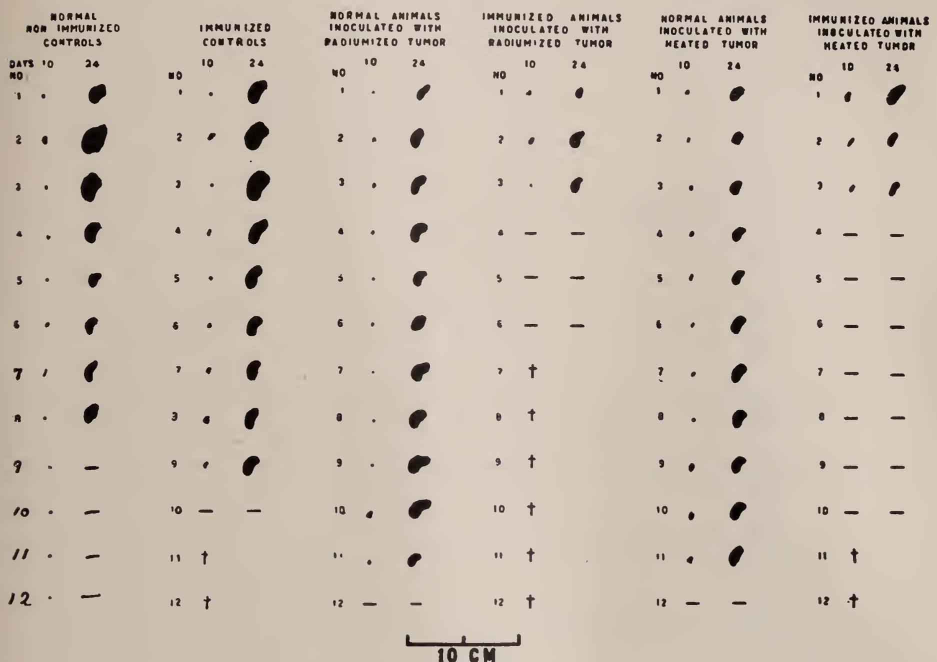

Chart 4. Ehrlich Mouse Sarcoma

Comparative influence of radium and heat previous to inoculation into immunized animals.

tumor showed an average of 62.75 per cent and those immunized and inoculated with heated tumor showed 81 per cent average immunity, an increase of over 100 per cent in both treated groups. As is shown in both the table and the charts, our results were not influenced by the type of immunizing material used. It will also be noted in the charts that the growth energy of the treated tumors was depressed, their size on a given day being smaller than the untreated neoplasms.

The fact having been verified that depression of growth energy renders tumors more susceptible to the immunizing power of homologous living normal cells, it was determined to investigate the influence of depression of growth energy upon other phases of immunity.

In the succeeding experiments radium was used to depress the growth energy.

TABLE 1

		TUMOR STRAIN							
		180		199		Ehrlich sarcoma		Jensen sarcoma	
		+	−	+	−	+	−	+	−
Normal controls inoculated with normal tumor	Number	88	1	20	7	16	10	18	1
	Per cent	99	1	74	26	61	39	95	5
Immunized controls inoculated with normal tumor	Number	60	16	13	9	9	1	14	11
	Per cent	78	22	59	41	90	10	56	44
Normal animals inoculated with radiumized tumor	Number	90	2	16	3	20	1	18	6
	Per cent	98	2	84	16	94	6	75	25
Immunized animals inoculated with radiumized tumor	Number	37	35	8	38	3	3	2	18
	Per cent	51	49	18	82	50	50	10	90
Normal animals inoculated with heated tumor	Number	17	2	17	6	21	1	13	10
	Per cent	89	11	73	27	95	5	57	43
Immunized animals inoculated with heated tumor	Number	4	8	0	14	3	7	8	16
	Per cent	12	88	0	100	30	70	34	66

\+ = takes.
— = no take.
Number = actual number of animals used.
Per cent = percentage of takes or immunity as the case may be.

That the resistance of a graft to concomitant immunity is decreased by radium is shown in the following experiment. Thirty-three rats bearing eighteen day old Flexner-Jobling carcinomata were divided into two groups. This tumor under ordinary conditions does not produce concomitant immunity. One group of eighteen animals received a second inoculation of 0.003 gram of the same tumor strain, the inoculated material having

been exposed to radium in the manner described in a previous paragraph. The second group of fifteen animals was inoculated with a similar dose of the same tumor not exposed to radium. A control group of ten normal animals was also inoculated with radiumized tumor.

The results, as depicted in chart 5, show 44 per cent concomitant immunity in the group inoculated with radiumized tumor,

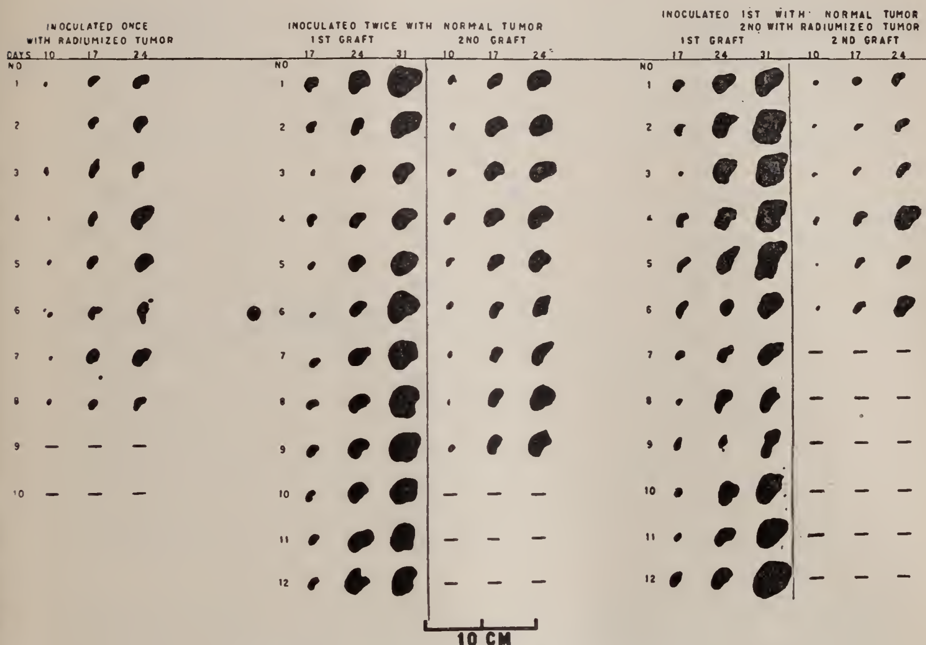

CHART 5. FLEXNER-JOBLING RAT CARCINOMA

Effect upon concomitant immunity of radiating second graft

as compared with 20 per cent concomitant immunity in the group inoculated with normal tumor. The normal animals inoculated with radiumized tumor also exhibited 20 per cent natural immunity, showing that radiation had not killed the tumor.

The influence of radium upon the processes of induced immunity was studied in still another experiment. A series of rats was inoculated with the usual dose of the Flexner-Jobling

tumor. Five days after inoculation, the stroma reaction being established, the skin over each graft was exposed for five minutes to 83 mgm. of radium element, unscreened. Upon the same day one-half of this group (36 rats) was injected with 0.05 cc. of rat spleen emulsion, the other half of the group serving as controls. The animals were immunized on the day of

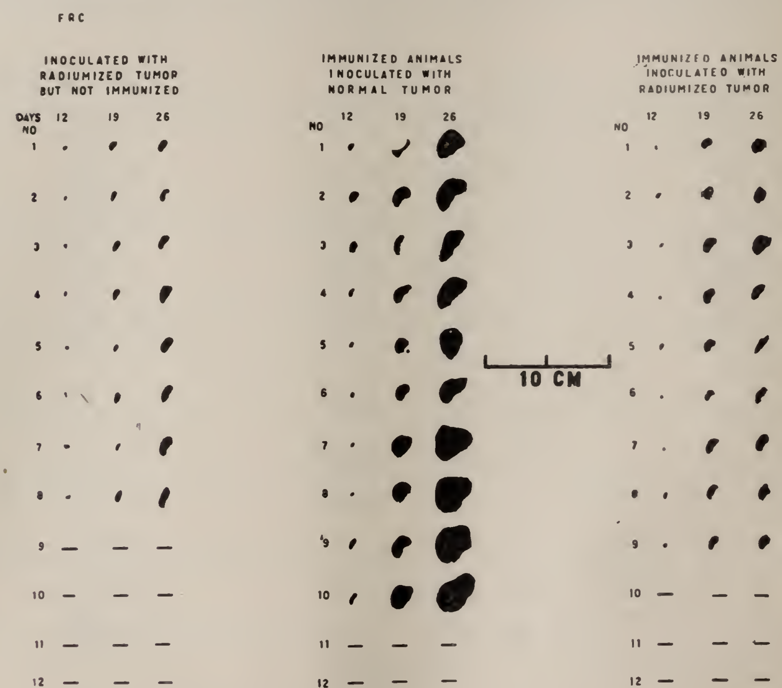

CHART 6. FLEXNER-JOBLING RAT CARCINOMA

Attempt to induce immunity after inoculation with radiumized tumor

radiation so that both radium and immunity might exert their maximum effect simultaneously, i.e., about the tenth day.

A further control group of 36 animals which had been inoculated at the same time as the other two groups was also immunized with 0.05 cc. of rat spleen pulp.

As is shown in chart 6, twenty-six days after radiation the tumors had disappeared in 25 per cent of those radiated and immunized, as compared with 27 per cent in those radiated but

not immunized. As the chart shows, the two groups with radiated tumors show inhibition of tumor growth as compared with the nonradiated animals, though radiation had not been sufficient to kill the tumor completely. A tumor having once been established, therefore, the retardation of its growth energy by radium does not make it any more susceptible to immunity than are growing tumors that have not been radiumized, a result in complete accord with the previous work of Russell (5), who used untreated tumor. As the established tumor which has been radiumized is not subject to immunity reactions, it is much less probable that the tumor which has not been radiumized is in any way sensitive to immunity reactions. This obser-

TABLE 2

	NO. OF ANIMALS	PERCENTAGE OF IMMUNITY
Normal animals with normal tumor	19	0
Normal animals inoculated with radiumized tumor	20	5
Immunized with mouse carcinoma, inoculated with normal tumor	20	10
Immunized with mouse carcinoma, inoculated with radiumized tumor	33	9
Immunized with autologous skin, inoculated with normal tumor	15	10
Immunized with autologous skin, inoculated with radiumized tumor	12	0

vation, therefore, casts doubt upon the power of radium or x-ray to affect metastases of tumors at a distance from the growth radiated, as has been repeatedly claimed by clinical workers. Clinicians have stated that the radiumization of a primary breast tumor causes nodules in the axilla to disappear, and have proposed the hypothesis that ferments are set free from the primary tumor under the influence of the radiumization which act in an unfavorable manner upon masses at a distance from the primary growth. The experiments detailed above, however, show that the shrinkage and disappearance of such nodules—if they really do disappear—must be due to some other influence than the hypothetical ferment. The very great suscepti-

bility of lymphoid tissue to even slight radiation is well known, and any change in the size of the lymph-nodes, even if they are invaded by carcinoma, may be due to reduction of inflammatory edema and to the destruction of the lymphoid elements, thus leaving the carcinoma untouched. This latter phenomenon has been repeatedly observed where clinical cures have been obtained of carcinomatous nodules, a marked shrinkage taking place upon relatively slight radiation. If such nodes are excised and examined, it is found that the lymphoid tissue has disappeared, but that the carcinoma, which forms only a small portion of the total mass, has remained as active in its growth as ever; and, in fact, those cases which have been followed have shown that ultimately recurrence takes place, even though the nodule after radiation was greatly reduced in size.

In a final experiment, the possibility of making tumors susceptible to attempts to immunize with heterologous and autologous tissue was investigated. Although some investigators have described the appearance of immunity after the introduction of heterologous tissues, the majority have not succeeded in confirming their results; and almost all are agreed that autologous tissues are powerless to confer immunity.

The Flexner-Jobling rat carcinoma was the tumor chosen for this experiment, the radiation, the inoculation dosage, and the methods being the same as those described in the early paragraphs of this paper. The animals were divided into several groups, the rats of the first series being immunized with 0.05 cc. of skin taken from the animals themselves, those of the second series with 0.05 cc. of mouse carcinoma, while those of the third series were not immunized. Ten days after immunization, one-half of the animals of each series were inoculated with untreated tumor, the other half receiving inoculations of radiumized tumor. Thirty-one days after inoculation, our results showed that exposure to radium did not make the Flexner-Jobling carcinoma susceptible to either autologous or heterologous tissues. The numerical data of the experiments are given in table 2.

CONCLUSIONS

Depression of the growth energy of a transplantable tumor by heat or by exposure to radium increases its susceptibility to the immunizing action of homologous living cells, whether they be normal or tumor cells. With the technic as described in this paper the additional immunity thus obtained may be 100 per cent over the usual figure.

The increased susceptibility of treated tumor to the immunizing power of living cells is not in evidence when autologous elements are employed, or when homologous tissues are introduced subsequent to tumor implantation.

Tumors which have established a residence in their hosts, i.e., have excited a stroma reaction and obtained a blood supply, are not influenced by retardation of their growth energy with radium and the simultaneous introduction of homologous living cells.

Thus, none of these results leads in any way to the conclusion that the improvement described in human cancer under radium treatment is due to the stimulation of autologous cells or that benefit is to be expected by radiumization and previous or subsequent injection of homologous lymphoid tissue. Even though the tumors employed in these experiments had been cured, the results could not have been transferred to man, where the problem is to cure a spontaneous (as distinguished from a transplanted) neoplasm. As an animal can not be immunized against its own tumor, or with its own tissues, it is readily seen that the application of such experiments as these to man can hardly lead to a profitable result.

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FLUCTUATIONS IN THE GROWTH ENERGY OF MALIGNANT TUMORS IN MAN, WITH ESPECIAL REFERENCE TO SPONTANEOUS RECESSION

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It is a generally accepted fact that transplanted animal tumors may fluctuate widely in their growth energy, the fluctuations varying from a temporary cessation of growth followed by renewed cellular activity to recession and complete disappearance of the tumor. Hence, warning has repeatedly been given against drawing deductions from the results of experimental therapeutic procedures in animals without proper consideration of these natural changes in the growth energy of tumors.

Though this is not widely known, the warning is applicable also to the spontaneous tumors of man, since fluctuations of a similar character are a not uncommon occurrence in them, as the reviews of this subject by Lomer, Mohr, Gaylord and Clowes, and others, amply demonstrate. Handley has well expressed the situation as follows:

> The progress of a cancer is normally accompanied by regressive or curative processes. The recorded cases of natural repair of cancer, far from being anomalous and exceptional, merely illustrate more strikingly than usual the natural laws which govern every case of the disease.

Indeed, the literature of cancer is rich in reports of the recession of malignant tumors after one or another type of medical treatment, the particular therapeutic procedure which is supposed to have brought about the recession in each case being at once hailed as a "cure," only to give rise to failure and disap-

pointment when tried out on a large group of cases. It is probable, therefore, that the isolated cases referred to are really spontaneous recessions and not therapeutic cures.

With the idea of emphasizing the frequency of variations in the growth energy of human tumors, and at the same time of seeking further facts bearing upon these variations in proliferative activity, the cases of marked recession or spontaneous cure recorded in the literature have been summarized, additional cases added, and the entire material subjected to analysis from the standpoint of our present knowledge of experimental cancer.

While numerous interesting, and possibly authentic, cases of recession of human malignant tumors are recorded previous to 1890 (2), many of these have been eliminated from the present survey because the correctness of the diagnosis is open to very grave question. The factor of diagnostic error in this connection was recognized as far back as 1852 (3).

A criticism affecting many of the reported cases is the absence of any statement of an histological examination. The importance of such an examination is clearly shown by Czerny, who has reported an instance of the spontaneous disappearance of a supposed sarcoma of the femur, which upon more detailed examination was shown to be chronic osteomyelitis, due to staphylococcus infection. While in some of the reports it is evident from the general context that an histological examination has been made, all that is definitely stated is some such inexact diagnosis as "undoubtedly cancerous," or "malignant."

The lack of histological examination emphasizes errors in diagnosis, particularly in those cases where syphilis is strongly to be suspected. Thus many of the older reports have to do with primary tumors of the liver; primary malignant tumors of this organ are comparatively rare, however, and it is more than probable that these reported tumors were gummata. Again, the much more recent surgical experience with syphilis of the stomach and its confusion with carcinoma, shows that the factor of error in diagnosis still warrants very serious consideration.

In the present review, cases obviously open to question regarding the correctness of the diagnosis have been omitted,

except when the case has been quoted by some one other than the original author. When others have considered the case as bona fide, it has been quoted, and the reason for disagreement given.

That different neoplasms vary in their growth energy is constantly recognized by all clinicians; thus it is well known that, as a class, basal-cell epitheliomata grow very slowly, while gastric carcinomata have a high rate of proliferative activity. The influence of age and of certain physiological states, like lactation and pregnancy, upon the rate of tumor growth are also well recognized, youth, pregnancy, and lactation favoring a high degree of proliferative activity. With the exception of advanced age, there are no clearly recognized conditions which tend to inhibit the growth of a neoplasm.

It can be definitely asserted that regressive changes varying from a temporary standstill to the complete disappearance of the tumor, whether it be of epithelial or connective tissue origin, may occur at any age period, in either sex, and irrespective of the location of the growth. Though no accurate data can be given for the frequency of complete regression, Bashford has estimated that it occurs about once in a hundred thousand cases.

There are several types of recession: so, for example, various neoplastic deposits may cease growing for a time and actually become to some degree smaller, only to assume their proliferation again at a later period; or any or all of the new growths may be completely absorbed and the patient be apparently cured.

The clinical conditions which have been associated with regression have been various, though it has become evident, at any rate, that the forces at work may be either local or general. In those instances where only certain groups of neoplastic cells recede, while others continue growing, the recession is best accounted for on the basis of some local tissue reaction. In others, however, where all the neoplastic deposits are absorbed, some reaction taking place throughout the entire organism offers the best explanation. Nevertheless, there has been so far no demonstration of any antibody or ferment in the body which might be assumed to effect such a result.

The local conditions associated with the recession of neoplastic deposits are recognizable for the most part only by microscopic examination. These histological changes have been thoroughly studied by many observers, though unfortunately, as is the case with much of the histological investigation of cancer, the problem has not been solved. Like other tissues, tumors may be the site of any of the various types of infection or degeneration, which may result in the death and subsequent absorption of the particular group of cells affected, though other neoplastic cells in the neighborhood continue to grow.

We shall not enter into a discussion of the various types of degeneration which may be followed by recession, except to note that necrosis followed by calcification is the type most frequently associated with spontaneous absorption. Degeneration or infection having occurred, the affected cells die and are removed by the body forces which are at work when similar changes occur in nonmalignant tissues. The defect is repaired by granulation tissue.

Where neither degenerative changes nor infection can be determined as having initiated healing, the process is slightly different. Several human cases have been studied in which fibrosis, occurring without explainable reason, has resulted in complete absorption of the new growth.

With transplanted animal tumors which are undergoing absorption, the first change noted is death of the neoplastic cell, occurring first in scattered areas and finally involving the entire tumor; subsequently the necrotic material is in part liquefied, in part removed by scavenger cells, and the defect is finally healed by granulation tissue. What causes this cell death is a much disputed point, none of the several theoretical explanations which have been offered having as yet the support of a clear cut experimental proof.

The general body reactions noted in man during tumor recession are of several different types. The greatest number of spontaneous regressions have occurred following incomplete surgical removal of the tumor, next in order of frequency during some acute febrile process, and least frequently in connection

with some profound alteration in the metabolic processes of the organism such as extreme cachexia, artificial menopause, or the puerperium.

When recession occurs after incomplete operation, search for a possible explanation becomes very confusing. The cases coming under this heading can best be explained by classifying them according to what has actually been done at the operation, and then considering the various possibilities under each subdivision.

In the first subdivision of this broad group come the cases in which neoplasms have partly or completely receded after a simple exploratory laparotomy, the only tumor removed having been a small piece for histological diagnosis. In some of the histories of this group it is definitely stated that immediately after operation a high temperature developed, which continued without remission for several days. In this, as in all the subgroups of this division, we must consider the influence of the anesthetic, for it is possible that the removal of blood and tissue lipoids by the anesthetic might be an important element in the disappearance of the growth, though Gaylord and Simpson (126) as a result of their experimental work with mice came to the conclusion that removal of blood lipoids by an anesthetic stimulated growth. With the single exception that some of the cases have had high fever, no other fact leading to an explanation can be gathered from the data available.

In the second subdivision come the cases in which complete extirpation was impossible, though a large portion of the tumor was removed. But since pericancerous inflammation may extend for some considerable distance outside the true tumor, and since this tissue often cannot be distinguished at operation from the tumor, it is possible, and even probable, that in not a few of these cases the inflammatory tissue has been mistaken for tumor. The tumor having been removed, the pericancerous inflammation subsided and what had been erroneously regarded as neoplastic tissue thus disappeared. Another possibility is, that after incomplete removal the necessary manipulations and ligations so interfered with the blood supply of the remaining malignant tissue that death occurred from malnutrition.

In the third subdivision, we have to deal with the question of heat externally applied. Practically all these cases are uterine carcinomata which, being surgically inoperable, were curetted and cauterized to ease the symptoms of discharge and hemorrhage. In some instances this operation was repeated several times. The inhibitory influence of heat (fever) upon the recurrence of neoplastic proliferation has been commented upon by many observers. Thus Krukenberg (4) has reported that patients with carcinoma of the uterus in whom fever appeared before operation showed recurrence in 48.3 per cent as compared with 58.5 per cent in those fever-free before operation. Lomer (85), in a most thorough and masterly survey, has drawn interesting deductions from the cases which he has compiled. It is true that the majority of the cases collected by him were uterine carcinomata, many of which were of the fundus and of a comparatively low grade of malignancy; still the period of freedom from recurrence after curettage and cautery, as recorded by this observer, is striking.

The occurrence of recession after acute infections has been commented upon in another paragraph. It has been shown experimentally (5) that comparatively low degrees of heat applied to animal tumors before inoculation, even for brief periods, distinctly retard the growth energy of these tumors, though others say that the growth energy is increased, and still others that heat has no effect. Bolognino (6), one of the many who has commented upon the relation of heat (fever) to spontaneous recession, has drawn attention to the fact that the amount of tumor still remaining before recession has occurred in the majority of cases has been small; however, as much as 375 sq. cm. of a cancer has disappeared. From the clinical standpoint, the important points in regard to heat are: (a) a temperature of from 104° to 105° F. (much lower than that of the actual cautery); (b) continuance of this for from forty-eight to ninety-six hours without remission.

The observation that a neoplasm may be absorbed subsequent to, or during, an acute infection, opens a most interesting field for speculation. The greater number of cases in this group have

occurred after an attack of erysipelas, an observation which has led to the use of toxins of the causative organism as a therapeutic measure. However, further observation shows that recession has also occurred after small-pox, pneumonia, malaria, and acute tuberculosis. No one organism is, therefore, specific in causing regression. In the histories of those cases that are given in detail, there is a common symptom, namely, high temperature, sustained without remission for several days. It is well to emphasize here that not every case of erysipelas, acute tuberculosis, or small-pox has a temperature as high as 104° F. continuously for from three to five days. Injections of bacterial toxins, while they do give rise to violent febrile reactions, are not characterized by the continuance of fever in full violence and without remission over a period of forty-eight hours.

Recession of growth during profound alterations in general metabolism is, in the present state of our knowledge, not susceptible of clear explanation. Those engaged in experimental cancer research have shown that animals in a poor state of nutrition are not good subjects for inoculation with tumor, the grafts either not growing at all, or proliferating very slowly and very often receding. This coincides with case reports reciting cessation or regression during cachexia. On the other hand, the recent study of Jaworski (7), made during the present world war, has shown that in man a deficiency of 50 per cent in the calories necessary to sustain equilibrium in weight, although it often results in the absorption of benign tumors such as myomata, may markedly increase the growth of malignant neoplasms. While poor health and cachexia are associated with loss of weight, emaciation due to starvation should not be construed as identical with cachexia or poor health. There is evidently some element other than the relatively simple one of food supply involved in the regressive change.

The influence of nutrition is more plainly shown in the several recorded instances of neoplasm arising during pregnancy and receding during the lying-in period. In two of the recorded cases, this sequence of events occurred in three successive pregnancies. It can be logically expected that an increase of nour-

ishment would cause rapid growth of a tumor, but the neoplasm having once started, why recession should occur upon a return to a more normal metabolic condition is, in the present state of our knowledge, unexplainable.

In another and smaller group, recession of a malignant tumor has followed the absorption of a transudate. These cases are best explained by cytotoxin or cytolysin formation, even though such antibodies have as yet not been demonstrated by experimental means. The spontaneous regression of chorioepitheliomata is quite possibly due to such antibodies, as the tumor cells are not strictly autologous, half being derived from the male in distinction to ordinary tumors in which the cells are completely autologous.

It may be concluded that recession of a malignant growth can occur in either sex, at any age period, with any type of malignant tumor, and irrespective of the location of the growth. It occurs after a variety of conditions, a proof that no particular one is specific, and it is very probable that all the conditions noted are preliminary, so to speak, and act by depressing the proliferative energy of the malignant cell until the defensive forces of the body (cytotoxins, cytolysins) are able to accomplish the final destruction. It appears that the most efficacious of all the many conditions which can bring about regressive change is heat, applied from without or occurring under the limited conditions of long duration and comparatively low degree.

The three examples which have come under the personal observation of the writer, and which are reported here for the first time, are given below.

The first, seen with Dr. J. A. Miller of New York City, is typical, there being many similar ones in the literature. It was a case of lymphosarcoma which underwent periods of recession, both with and without treatment, but subsequently terminated fatally.

Case 1. The patient was a Hebrew, forty-five years of age, whose occupation was that of clothing salesman. He was married and had three healthy children; his past and family history gave no facts ap-

plicable to his present condition; his habits, as regards alcohol and tobacco, were good, and he denied a veneral infection. On April 26, 1916, he first consulted Dr. Miller, complaining of pain in the left thigh and buttock. Upon physical examination, the anterior and posterior cervical chain of lymph nodes were found enlarged, and there was a mass the size of a walnut in the left pectoral muscle. The patient had noticed the lymphatic enlargement for five days, but had not paid much attention to it. On that day, his blood count, urine, and temperature were normal, and the Wassermann reaction negative. On April 28, the largest of the cervical lymph nodes, which was about 2 cm. in diameter, was excised, and a histological diagnosis of lymphosarcoma was made by the writer; this diagnosis was confirmed by Dr. F. C. Wood. The cervical lymph nodes continued to enlarge as did the mass in the pectoral muscle.

On May 5, 1916, he was admitted to the General Memorial Hospital. The diagnosis of lymphosarcoma was confirmed and enlarged retrosternal nodes were demonstrated in radiographs. Coley's fluid was given without result, and the patient was discharged May 24, 1916, unimproved. Between the date of his discharge and August, 1916, he had repeated x-ray treatments. Late in August he was seen by Dr. Harlow Brooks, who also confirmed the diagnosis of lymphosarcoma.

In September, 1916, he was admitted to Lebanon Hospital and treated with salvarsan in full dosage. The Wassermann reaction was negative on five different examinations, both with and without provocative treatment. At the time of his admission to Lebanon Hospital, all his nodes, cervical and inguinal, were much enlarged, and the mass in the pectoral muscle had increased greatly in size. After antisyphilitic treatment, all the nodules except the mass in the pectoral muscle subsided; this mass was removed and a histological diagnosis of lymphosarcoma made. After leaving the hospital, he remained well for six weeks, during which time he received salvarsan every ten days, as well as intramuscular injections of mercury.

On January 2, 1917, his conditions was as follows: He was very much weakened and jaundiced. The nodes on both sides of the neck were enlarged to a diameter of about 5 cm., and his spleen was palpable at the umbilicus. At the site of removal (left pectoral muscle) a recurrence about 5 cm. in diameter was present, and a mass was found in the epigastric region also, approximately 10 cm. in diameter. Examination of the blood showed nothing but a moderately severe anemia.

His condition steadily grew worse, all of the enlargements increasing in size and new involvements of the inguinal nodes appearing. This condition persisted up to February 16, 1917, when suddenly all the tumors disappeared overnight (observations twenty-four hours apart) the spleen receding to the costal arch, and the mass in the abdomen becoming decidedly smaller. This recession persisted for one week, when an increase in size again occurred, the nodes having attained before his death on March 5, 1917, a size comparable with the conditions present before recession set in. No autopsy was obtained.

Repeated examinations of the blood made during the last month of life showed no evidence of leukemia in either the total white count or in the differential count of the leucocytes. With the exception of the last day of the disease, the temperature was normal throughout his illness.

The second case observed by the writer emphasizes one of the fallacies to be guarded against.

Case 2. The patient was a female, seventy-five years of age, who had suffered from five cerebral hemorrhages and was as a result bedridden. During the second year of her stay in bed, a nonulcerated mass developed at the outer canthus of the right eye, projecting about half a centimeter above the level of the skin. This gradually increased in size until at the end of two years' growth it had reached a diameter of 2.5 cm. A clinical diagnosis of epithelioma was made and the use of radium suggested, a V-shaped section being removed for diagnosis; at the time of removal, there was rather free hemorrhage which was stopped by ligature. The histological diagnosis was squamous-cell epithelioma. Seven days after the operation, the tumor commenced to recede and within another week disappeared. Five weeks later the patient died of pneumonia.

At autopsy, the site of the tumor was removed en bloc, and serial sections were made. Examination showed that a large blood-vessel entered the neoplasm at the line of incision for diagnosis, and that the disappearance of the growth had probably followed obliteration of a major portion of its blood supply.

Case 3. This case occurred in the practise of the late Dr. A. V. Deuring. The patient, a female aged fifty-seven, had been under my (G. L. R.) observation for eleven years. When she was thirty-seven years old (twenty years ago) she had backache, obstipation, loss of weight, and bearing down pains, and a physical examination carried

out at that time showed a large irregular mass apparently arising from the left side of the pelvic girdle. At an exploratory laparotomy, an inoperable condition was found; there was a mass estimated to be the size of an adult head arising from the lateral wall of the left pelvis, and to it the descending colon and sigmoid were firmly attached, while scattered over the peritoneum were innumerable secondary growths. One of these was removed from the omentum, but further than the extirpation of this piece no surgery was attempted. Microscopical examination proved the tissue to be a typical spindle-cell sarcoma.

Subsequent to the operation, a marked sciatic neuritis developed on the right side (pressure or metastasis?). For the sciatica, and without any idea of influencing the growth, the patient was given hot air baths (baking), the entire body being treated; thirty such treatments in all were given. To the surprise of all, instead of growing progressively worse the patient slowly improved until her health was completely restored two years after operation, the pelvic mass having also disappeared. In 1913, a blood Wassermann was negative, and in 1916, a luetin test was also negative. In December, 1916, the patient died of uremia. At autopsy, the anatomical diagnosis was pulmonary edema, mitral endocarditis, and chronic interstitial nephritis. There was no demonstrable lesion in the pelvis or in any of the abdominal viscera to indicate the former presence of a neoplasm.

Including those recorded in this paper, the writer has been able to collect a total of 302 cases in which recession, either temporary or permanent, has occurred in a malignant growth. These have been divided into three main groups: Group I consists of those reports which stand a most rigid scrutiny; group II contains those cases in which some slight question may be raised regarding the adequate control of all possible diagnostic errors, while the cases included in group III comprise those open to more or less grave doubt as to the correct diagnosis. Each of these main groups has been subdivided into (a) the group of complete recession, and (b) that of partial recession.

All the cases quoted below have been verified by a reading of the original article. There are still others in the Swedish, Russian, and Italian literature, but, the original articles not being available, these have not been quoted.

The criticism may justly be made that in many cases the period of observation has been too brief to permit the word cure to be used. Such criticism is beside the question; the fact remains that recession did occur, and the duration of such recession is not important from our present standpoint.

GROUP I

a. Complete recession of malignant tumor, carefully controlled

In the following paragraphs, the cases coming under Group I, subdivision (a), are briefly abstracted.

Mathews (8): A case of melanosarcoma originating in a pigmented mole of the back and involving the axillary nodes. The primary tumor and portions of the axillary nodes were removed, and the diagnosis confirmed by microscopical examination of both. Immediate return of the tumor was confidently expected, but, at the date of the report, the patient has been clinically well for two years. In a personal communication, Mathews states that the case was still free of recurrence three years and six months after operation.

Handley (9) has reported histological changes, which were recessive in character, in the metastatic deposits of a case of melanosarcoma. In his case, however, these changes did not progress to the degree of clinical manifestation.

Schuchard (10): An advanced carcinoma of the stomach, in which the organ was resected even though there were widespread peritoneal metastases with typical chyliform ascitic fluid. The diagnosis was confirmed histologically. Two and one-half years later this patient died; the autopsy showed no local recurrence, the peritoneal metastasis and ascitic fluid, also, having been absorbed. Pleurisy is given as the cause of death.

Godfrey (11): A case of carcinoma involving the tonsil and base of the tongue, so extensive as to be inoperable. The diagnosis was confirmed by microscopical examination. The patient was sent home to die, the only treatment given being antiseptic mouth washes. When seen, eighteen months later, there was no trace of the original tumor.

McKay (12): A scirrhous carcinoma of the breast, diagnosed microscopically, was removed in 1904. In January, 1906, there was a local recurrence which was treated with x-ray. The disease gradually

progressed until in August there was a pleural effusion and involvement of the opposite breast, the patient at that time being in a desperate condition. She continued to be practically moribund until December 28, 1906, when a sudden and overnight improvement occurred with the rapid absorption of the entire tumor area. Three weeks later the patient died (92).

Noble (13): A case histologically diagnosed as chorioepithelioma. The tumor had perforated the fundus uteri and was attached to the bladder. During the course of a hysterectomy, it became necessary to leave a portion of the tumor attached to the bladder. Examination sixteen months after operation showed that the patient was clinically well, and that no mass was palpable. Convalescence was febrile for six days.

Watson (14): A tumor directly beneath the chin was removed and examined histologically, the diagnosis being round-cell sarcoma. Later the tumor recurred in both right and left cervical chains of lymph nodes, and those on one side were removed. During convalescence from this operation, a violent attack of erysipelas occurred. Subsequent to the attack of erysipelas, the nodes on the other side spontaneously receded.

Gould (15): A carcinoma of the left breast was removed, and the diagnosis was confirmed histologically. A salpingo-oöphorectomy was performed five months after the breast was amputated, and shortly thereafter appeared a recurrence in the breast scar and in the supraclavicular nodes. Two and a half years later there were other recurrences and metastases, the liver also being much enlarged; at that time the patient was feeble and emaciated. For the next few years no treatment was given, yet the liver became smaller and all the recurrences disappeared except a small one in the breast scar. Subsequently the patient entirely recovered.

Weindler (34): Three cases, all of which were diagnosed microscopically. One was a glandular carcinoma of the fundus of the uterus, the other two were cervical uterine carcinomata. In all the cases, the treatment was curettage and cauterization. The patients, all of whom were inoperable cases when first seen, were clinically well from six to seven years after the palliative operation.

Ladinski (125) has collected a series of cases of undoubted carcinoma of the uterus (verified microscopically) which were apparently cured by a simple curettage. In eighteen of these, the curettage was followed by hysterectomy; in four no hysterectomy was performed.

Six of the cases were free of recurrence from six months to four years; in five the period of cure was not given.

Boldt (35): A case of inoperable abdominal carcinoma (the diagnosis being verified by histological examination of the involved omentum) was autopsied "some years later" and no carcinoma found.

Marchand (39): A case of chorioepithelioma, which had perforated the uterine wall and involved the pelvic tissues, the uterine vein being thrombosed by tumor emboli. The diagnosis was confirmed by histological examination. Incomplete removal of the tumor was the only surgical possibility and this was done. One year later, the patient died, and at the autopsy no recurrence was demonstrable.

Riesel (116): A case of chorioepithelioma with an atypical microscopic picture. There was invasion of the superficial uterine muscle. The patient remained well one year after a very thorough curettage.

Bolognino (40): A case of round-cell sarcoma of the axilla, with histological confirmation of the diagnosis. The tumor recurred after removal, the recurrence being removed incompletely by curette. Ten days after the curettement a very severe attack of erysipelas supervened and the tumor remnants disappeared. Thirteen months later, there was no return of the neoplasm.

Ibotson (41): In 1914, a female aged forty-five years had her breast amputated for carcinoma. In 1916, there was a recurrence in the scar and metastasis had occurred in the uterus; no further surgical interference was deemed advisable. In February, 1917, the nodules in the scar had disappeared, and the uterus had returned to a clinically normal condition. The author has also reported other cases in which recession followed oophorectomy.

Prochownik (59): Two cases of uterine carcinoma, both diagnosed microscopically, and considered inoperable. In order to relieve the symptoms of hemorrhage and discharge, both of the cases were curetted and cauterized. Upon examination, four and six years after operation, both cases were clinically free from all evidences of carcinoma.

Littauer (60): Six weeks after an abortion, there occurred irregular periods of bleeding from the uterus. Physical examination showed a mass "the size of a cherry" in the posterior wall of the uterus; this mass was removed and a histological diagnosis of chorioepithelioma was made. No hysterectomy was performed. Ten weeks later a second curettage showed no histological abnormalities. One year later, the patient was clinically well.

Grofe (61): A case of chorioepithelioma localized in a small area of the uterus, the tumor being palpable and a small piece having been

removed for histological diagnosis. Eight days later, the entire uterus was removed, and though it was cut in serial section no tumor could be demonstrated.

Langhans (62): A nodule which developed in the vagina after accouchement was removed for microscopic examination and found to be a chorioepithelioma. The nodule recurred in fourteen days, but shortly thereafter it suppurated and healed. Ten months later the patient was well.

Horman (63): A woman seven and a half months pregnant aborted. She was curetted, microscopical examination of the curettings showing chorioepithelioma. Shortly afterwards metastasis appeared and she was sent home to die. One year later, both the tumor and metastasis had disappeared. Subsequently she had a normal pregnancy.

Guinard (113): A case of carcinoma of the breast complicated by a uterine fibroid. Castration was performed during a hysterectomy. The breast tumor completely receded.

Three cases of malignant growths, in which castration was followed by recession, are quoted by Beatson also (118).

Johr (115): A sarcoma of the axilla with many metastases; the diagnosis was confirmed microscopically. The woman was pregnant and an abortion was induced, whereupon all the masses disappeared. Death occurred six weeks after absorption of the growths.

Lilienthal (119): An intercostal recurrence of a mammary carcinoma verified microscopically, which receded completely. This case, to the personal knowledge of the present writer, is still free of recurrence seven years later.

Powers (123): A fibrosarcoma of the skull, histologically diagnosed, which receded, together with its secondary deposits, after partial removal.

Kutzner (67): An eighteen-year old girl with a round-cell sarcoma of the breast had many metastatic deposits in the subcutaneous tissues of the body. The diagnosis was confirmed by histological examination. She developed an acute infection of the lung (pneumonia?) and all of the neoplastic deposits disappeared.

Kleeblatt (68): A case of primary lymphosarcoma, behind the auricle of the ear, and inoperable when seen. The diagnosis was confirmed by microscopical examination. The patient was purposely inoculated with erysipelas and complete recession of the tumor followed.

Fleischmann (69): Two and a quarter years after the delivery of a hydatiform mole, nodules were found in the vaginal wall and uterus.

The vaginal nodules were removed and examined histologically, the diagnosis being chorioepithelioma. Ten months later, there was no evidence of recurrence.

Lick (70): An inoperable uterine carcinoma, microscopically diagnosed. The case was curetted and cauterized. Four years after operation, there was no return of symptoms and examination of the uterus showed a normal condition.

Jordan (82): An epithelioma of the cervix, which was histologically diagnosed, was treated with cautery and curettage. The entire uterus was removed two and a half years later, and when examined microscopically, no tumor could be found.

von Franque (83): A case of chorioepithelioma was curetted. The diagnosis was made by microscopical examination. For several days the patient had a temperature of 41°C. Twenty-nine days later, she was again curetted and no chorioepithelioma was found in the curettings. Subsequently she bore two healthy children.

Another case of chorioepithelioma verified by two curettages with histological examination. Twenty days after the last curettage, a hysterectomy was performed. The uterus was cut in serial sections and no chorioepithelioma found.

Gould (84): A carcinoma of the superior maxilla, verified by histological examination, recurred three months after operation. The recurrence was inoperable. Three months later, without any treatment, the recurrence had been completely absorbed.

Lomer (85): A case of carcinoma of the uterus, in which, during removal of the uterus, the broad ligaments were found infiltrated with tumor. In spite of incomplete removal the patient was well seven years later and there was no evidence of malignant growth.

Lomer has collected a series of 213 cases of recession of malignant growths, occurring chiefly after the application of the cautery; his article is intensely interesting and well worth study. Of the cases quoted by him, 10 have been considered separately in this abstract, and 103 have been excluded from consideration because of lack of detail or evident error in diagnosis; the remaining 100 have been accepted as *bona fide*. Of these 100 cases, 40 fall under the present group I (a); of the remainder, 20 come under group I (b); 17 under group II (a); 15 under group II (b); 8 under group III (c). They have not been quoted individually.

Clarke (86): An inoperable carcinoma of the stomach with metastasis in the mesenteric nodes verified by histological examination. The patient was perfectly well nine years after an exploratory laparotomy.

Chrobak (87): A case of carcinoma of the cervix uteri with a histological diagnosis. Eleven years after curettage and cautery, the patient was well and without evidence of tumor.

A case of carcinoma of the uterus, verified microscopically, which was curetted and cauterized in 1884; the patient was still well and tumor free in 1905.

Proescher (96): A carcinoma of the gall bladder, microscopically verified. The gall bladder was drained. The fistula persisting the patient was again operated several months later and the gall bladder removed. Histological examination of the gall bladder showed replacement of the entire carcinoma with hyaline masses; no tumor cells were demonstrable.

Martin (108): A female, forty years of age, with an epithelioma of the cervix verified by microscopical examination. Operation was refused. Twenty-two years later, the patient was alive and well without evidence of tumor.

Bretschneider (24): An inoperable carcinoma of the uterus, the diagnosis being confirmed microscopically, was curetted and cauterized. One year later the patient had so improved that a radical operation was unsuccessfully attempted. Curettage and cautery were again employed. The curetting from the second operation also showed glandular carcinoma. One year after the second operation the patient was clinically well.

b. Partial recession of malignant tumor, carefully controlled

Brief abstracts of the cases falling in this group are given below:

Rotter (32): A female of thirty-one, with the clinical diagnosis of polyposis of the rectum complicated by an adenoma malignum, the diagnosis being confirmed histologically, was operated upon and the tumor removed. Recurrence took place in three months, the histological diagnosis of the recurrence being the same as for the primary tumor. The first recurrence was removed only to be followed by a second one which was not removed. Six months after the last opera-

tion, the patient was clinically cured. Death occurred three years after the last operation. At the autopsy, it was found that the rectal tumor had competely disappeared, the only remaining evidence of malignancy being a small metastasis in the iliac bone. Histologically this metastasis was of the same type as the primary tumor.

Bolognesi (16): A case of multiple basal-cell epitheliomata of the face and lip, in a woman. The diagnosis was made histologically. One of the multiple growths completely receded. A biopsy of the healed lesion showed an extensive and marked fibrosis.

Dahmen (18): A case where at autopsy a primary carcinoma of the stomach was almost completely healed, though there were enormous metastases in the liver.

Schwarz (5): An epithelioma of the head arising from a sebaceous cyst in which healing was taking place. The recession, however, was only demonstrable histologically.

Martin (120): An epithelioma of the eyelid, almost completely healed as a result of calcareous degeneration.

Gravers and Price (52): A case of hemangioendothelial blastoma occurring in the mouth of a young negress. The tumor developed during her first pregnancy, and almost completely receded during the lying-in period. The tumor was finally removed, but recurred.

Hodenpyle (57): A case of recurrent carcinoma of the breast with metastases in the liver which receded after the appearance of a chyliform ascitic fluid. The patient subsequently died of carcinoma.

Butlin (58): A case of metastatic epithelioma in the lymph nodes of a chimney sweep. A thorough examination failed to show any malignant or other growth on the scrotum or elsewhere in the body. The primary tumor had evidently completely receded.

Watson (19): A case of pedunculated neoplasm of the back in the region of the scapula occurring in a female thirty-six years of age. The tumor was removed but not examined histologically. Four days after operation, the growth was as large as before operation, though not pedunculated. Portions of the recurrence were removed and examined histologically, the diagnosis being round-cell sarcoma. Seven days later an unsuccessful attempt was made to remove the recurrence. The convalescence after the second operation was febrile. One year later, the tumor was much smaller, approximately the size of the original growth and again pedunculated.

Wells (20): A case of carcinoma of the uterus, verified by microscopical examination, and found by exploratory laparotomy to be inoper-

able. Four and a half years after operation, the tumor had infiltrated the vagina. One year later the patient died and at the autopsy the peritoneum was found studded with small whitish areas, while the primary tumor had disappeared. Histological examination of the whitish areas covering the peritoneum showed carcinoma with extreme calcareous infiltration.

Jacobsthal (17): A case of epithelioma in a male forty-five years of age. Because of the peculiar clinical appearance of the growth the tumor was cut serially, and it was found that the malignant tissue itself consisted of a ring shaped area, the central cavity of the ring being filled with a dense connective tissue. This histological picture is interpreted as showing that the central portion of the growth had healed, though the periphery had kept on growing.

Handley (48): Four cases in which spontaneous fracture of bones occurred following metastatic tumor formation. Although all the cases subsequently died of the malignant condition, the fractures healed and the metastatic tumors which gave rise to the fractures disappeared.

Longcope (25): A male in whom tumors of varying size were found at operation scattered throughout the peritoneal cavity, chiefly in the gut and mesentery; the condition was considered inoperable, and the abdomen closed. Directly after the operation, the patient improved for a period, then died. At autopsy, it was found that most of the nodules had almost disappeared, though histological examination showed diffuse lymphosarcoma in practically all the abdominal viscera.

Osler (22): A carcinoma of the breast was removed in 1897. One year later, secondary deposits appeared in the right eye, and there were also metastases in the sternum, and a pleurisy with effusion. Paraplegia due to spinal cord metastasis developed, the patient becoming very much emaciated and being confined to bed for months. In 1900, recession had so far advanced that the paraplegia had disappeared and the ocular symptoms had so improved that sight was to some degree restored. The sternal metastases, furthermore, had been absorbed. The patient was able to go about at this time, but eventually died of carcinoma.

In a second case, a breast was removed for carcinoma in 1898. In 1899, a spinal cord metastasis developed, causing a complete paraplegia. There was also a recurrence in the scar and in the lymph nodes of the neck. Both the paraplegia and the other secondary in-

volvements temporarily entirely disappeared; eventually, however, the patient died of carcinoma.

Gould (21): A scirrhous carcinoma of the breast, diagnosed microscopically, recurred two years after operation. The recurrence was removed, but another developed two years later. The second recurrence was removed, the menopause occurring at the same time. A third recurrence developed and with it metastasis in the chest and femur. The patient then apparently became moribund, and the various neoplastic deposits disappeared. Recession was temporary, however, death occurring several years later of carcinoma.

(Footnote in original article (23)): A woman of thirty-six years of age, who had had several children, was again pregnant seven months, when masses developed in the breast, axillary nodes, introitus of the vagina, uterine cervix, and in the pouch of Douglas. An abortion was induced with glycerin, and ten days afterward all the masses, except that in the cervix, had disappeared. This mass was removed and examined histologically, the diagnosis being sarcoma of type not specified. Six weeks later the patient died suddenly in collapse. There was no autopsy.

Schkarin (71): A case of round-cell sarcoma in a six year old girl. At the time of operation, the peritoneum was found greatly thickened and there were innumerable metastases scattered over the peritoneum and mesentery. Part of the peritoneum and one of the metastases were excised and examined histologically, the microscopical diagnosis of round-cell sarcoma being made. The condition was so far advanced that the primary tumor could not be definitely located at the operation. For four days after operation, the patient had a violent fever and then died. At autopsy, a round-cell sarcoma of the jejunum 2.5 cm. in diameter was all that was left of the extensive involvement found at operation. The temperature was not due to sepsis.

A five year old child with a tumor in the sternum and in the abdomen. Five days after an exploratory laparotomy both masses disappeared, only to recur and cause death four weeks after operation. The histological diagnosis was sarcoma.

Walsche (72): A carcinoma of the breast of two years' duration. A cerebral metastasis producing the symptoms of apoplexy occurred, which caused death ten weeks later. At autopsy, the primary tumor was found completely absorbed, though the metastasis in the brain was evidently growing.

Kaposi (117): A tumor of the upper jaw with multiple skin metastases. A piece was excised for histological examination, the microscopical diagnosis being lymphosarcoma. All the skin metastases quickly disappeared after the excision of the piece for diagnosis. Death subsequently occurred from lymphosarcoma.

Peterson and Colmers (105): A carcinoma of the pylorus, which was resected, several carcinomatous nodes being left behind. The diagnosis was confirmed by histological examination. One and a half years later, the patient died of intestinal obstruction due to an umbilical hernia. At autopsy, the cancerous lymph nodes had disappeared though there were small metastases in other organs.

Saar (104): While studying the regressive changes of the breast associated with senility, this author discovered a minute carcinoma undergoing recessive alteration.

Randolph (101): An endothelioma of the arm of three years' duration, growing very rapidly in the last six months, was removed. Histologically, the tumor showed a subsiding acute inflammation which was leading to fibrosis and healing.

Friedman (93): A tumor of the lip which receded completely, only to be followed by involvement of the lymph nodes. Removal of the affected nodes showed metastatic carcinoma, the primary tumor having healed completely. Death occurred from carcinomatosis.

Wells (92): A carcinoma of the breast exhibiting recessional changes in the metastases after the primary tumor had been removed.

Cleland (111): An epithelioma of the neck in which distinct recession and healing were demonstrable histologically.

Merkins (quoted by Hendry (110)): A carcinoma of the lip which had completely healed, though there were metastases in the regional lymph nodes.

Eissemenge (114): A case in which tracheotomy was done to relieve the dyspnea produced by a round-cell sarcoma of the tonsil. The tumor completely disappeared. Metastases in other regions finally caused death.

Handley (121): A carcinoma of the breast of twenty-eight years' duration, in which secondary deposits repeatedly disappeared.

Gould (122): Almost complete recession of a carcinoma of the breast after oöphorectomy.

GROUP II

a. Complete recession of malignant tumor, open to slight question

The cases coming under this group are abstracted below:

Bolognino (26): A case of adenocarcinoma of the testis which previous to operation had been treated ineffectually with potassium iodide. After operation, a metastasis developed in the opposite testis. This metastasis became ulcerated and an attack of erysipelas followed, after which the tumor disappeared, only to recur later. This time the recurrence was partly removed, and ten days later, a second and violent attack of erysipelas occurred. Ten months afterward the remaining tumor had entirely disappeared.

Czerny (27): In resecting a sigmoid for carcinoma, the line of excision passed through cancerous tissue. In spite of the incomplete operation, the patient was free of symptoms five years later.

In resecting a carcinoma of the colon in which the tumor was adherent to the small gut, part of the tumor was left behind. Four years later the patient was clinically well. These tumors, of course, might have been due to a diverticulitis of the gut, the inflammatory and hyperplastic lesions of which often are called malignant.

Theilhaber and Edelberg (28): Three cases of carcinoma of the uterine cervix, in which it was not possible totally to remove the tumor, portions of involved broad ligament being left behind. These cases were clinically well seven, five, and four years respectively, after operation.

Sigg (66): A tumor of the breast, together with enlarged axillary nodes, was extirpated; the growth is said to have been "malignant." One year later there was a recurrence, which was removed, and a second recurrence took place six months afterward. Shortly thereafter, the patient developed pulmonary tuberculosis, and, as this disease advanced, the neoplastic tissue was absorbed completely. Death occurred from tuberculosis. There was no autopsy.

De Gaetano (74): A patient with an epithelioma over the left frontal eminence was attacked by erysipelas two years after the onset of the tumor; the growth disappeared, to return three years later, following trauma at its former site. This recurrence was twice removed, reappearing, however, each time. After the last recurrence there occurred a violent attack of erysipelas, and this was followed by final disappearance of the tumor.

Koster (88): A sixteen year old boy, with a tumor of the orbital fossa, to whom iodide of potash had been given without result. The histological diagnosis was sarcoma. Only a portion of the tumor could be removed. Five years later, the tumor had completely receded and the patient was entirely well.

Warring (89): An inoperable carcinoma of the gall bladder, verified microscopically, which receded, the patient being alive and free of all symptoms two years after an exploratory laparotomy.

An inoperable carcinoma of the caecum, verified microscopically, the patient being alive and well seven years after an exploratory laparotomy.

Loeffler (90): A case of carcinoma of the breast, verified microscopically, which receded when temperature (fever) occurred during the course of a malaria.

Riffel (91): An epithelioma of the face which receded after an attack of small-pox.

Schlimpert (53): A case of tumor of the liver which was entirely removed, the histological diagnosis being epithelioma. At the time of operation, radiographs showed shadows in the lungs which were taken to be metastatic deposits. Three years later, the lung shadows had disappeared and there was no recurrence of the liver tumor. Whether this tumor was primary in the lung or in the liver is immaterial from the standpoint of the present review.

Zagger (29): A male, with a papilloma of the gum, noticed that the tumor was suddenly commencing to grow rapidly. When first seen by the physician, the tumor was as large as an egg and inoperable. A portion of the growth was removed for histological diagnosis, the report being "malignant." The patient became extremely cachectic and finally almost moribund, in which condition he remained for six weeks. The tumor completely receded during this period, and the patient then recovered his usual good health.

Brettauer (30): A carcinoma of the uterus, in which the uterine arteries had been ligated when the intended operation (hysterectomy) had to be abandoned because of the collapse of the patient. Since then, time not specified, the patient has been well.

A carcinoma of the cervix curetted and cauterized repeatedly, the patient being reported as clinically well.

A carcinoma of the ovary found to be inoperable by exploratory laparotomy. The patient was alive and well two years later.

Webb (73): A carcinoma of the lip was twice operated on, and again

recurred; the third recurrence was inoperable. The final metastasis receded and had not recurred eight years later, when the patient died.

von Hansemann (107): A malignant adenoma of the rectum (diagnosis confirmed histologically) which at first grew rapidly, but then receded completely, disappearing eight years after the onset.

Hall (103): A hypernephroma within the capsule of the kidney, the tumor being entirely necrotic.

Fleischmann (102): A carcinoma of the cervix, microscopically confirmed, in which part of the tumor only was removed. There was profuse postoperative bleeding followed by temperature. Eleven years later the patient was free of recurrence.

A carcinoma of the cervix, microscopically confirmed, with incomplete operation; the patient was free from recurrence eleven years after operation.

Perrin (97): A carcinoma of the breast which receded after an operation for goiter. The operation wound had become infected and extensive suppuration with high temperature had followed.

Richardson (95): A male of thirty, with a carcinoma of the bladder, verified microscopically, was operated and the tumor removed. Shortly thereafter the tumor recurred, but the patient refused further operation. Two years later, the tumor had disappeared, and four years later there was no recurrence.

Wells (92): A male of sixty-three, with a colloid carcinoma of the caecum in the region of the appendix. It was declared inoperable and nothing was done at the exploratory laparotomy. One year later, he was again operated on for fecal fistula and it was found that the cancer had become calcified. Thirteen years after the first operation death occurred; the autopsy disclosed an extensive colloid carcinoma involving all the abdominal viscera.

b. Partial recession of malignant tumor, open to slight question

The succeeding paragraphs give in abstracted form the cases classed under this heading:

(Footnote in original article (36)): A female, during her first pregnancy, noticed a tumor in the breast which grew rapidly during the pregnancy, but which subsided almost to the point of complete disappearance during the lying-in period. She again became pregnant and the neoplasm grew as before, but did not recede to the same degree during the lying-in period. A third pregnancy occurring, the

tumor again grew rapidly but this time did not recede at all. Death supervened, and the histological diagnosis at autopsy was sarcoma, type not specified. It may be asserted that it was only during the last pregnancy that the tumor really became malignant, an objection which cannot be answered.

Williams (37): A case with enlarged lymph nodes in the neck, histological examination showing metastatic epithelioma, though there was no evidence of tumor in any region of the body. The inference is, that the primary tumor had completely healed.

Quossow (38): An eleven year old boy had a mass on the right side of his throat so large as to cause dyspnea. A tracheotomy was performed and the tumor disappeared in nine days, only to recur subsequently with metastasis. The histological diagnosis at autopsy was a polymorphous-cell sarcoma.

Williams (106): Seven cases of carcinoma of the breast in which the primary tumor receded while the secondary deposits progressed and killed the patient. Such recession may be due to a central necrosis from vascular thrombosis with absorption of the necrotic tissue.

Graham (94): A carcinoma of the breast, microscopically verified. The primary tumor was removed, and at death six years later healing by fibrosis was taking place in all the metastases.

GROUP III

a. Complete disappearance of malignant tumor, poorly controlled

The cases coming under this classification are abstracted below:

Mundi (50): A case of carcinoma of the vagina in a young girl which spontaneously receded. No further details are given.

Sanger (54): A case of epithelioma of the cheek due to a sharp tooth. The tooth was extracted and one-half the tumor removed for examination. The microscopical diagnosis was epithelioma. The portion of the tumor which was not removed disappeared in four weeks. Gaylord and Clowes, in their summary, consider this case as "bona fide;" however, syphilis has not been excluded. The histological picture resembled more an atypical epithelial proliferation, such as is often seen in wound healing and is more exactly duplicated by Scharlach R (55), than it does an epithelioma.

Crosbie (56): A tumor said to be malignant, in a male seventeen years of age. The neoplasm presented itself as an ulcer the size of a "sixpenny piece," having raised edges and numerous warty nodules; a portion was excised and reported as "malignant." The patient at the same time had an eczema (?). Eight months later, both tumor and eczema disappeared. Gaylord and Clowes consider this also as a "bona fide" case, but the histological description and the strong suspicion of syphilis have not been properly controlled.

Klotz (64): Six cases of carcinoma of the uterus with palliative operation, curettage, and cautery. The tumors are said to have disappeared.

Frankel (65): Three cases of uterine carcinoma treated with cautery and curettage. The tumors are described as having disappeared.

Both of these reports (Klotz and Frankel) are given later notice by Lomer (85).

Haidenhain (47): A case of ovarian tumor with peritoneal metastasis; there is no histological diagnosis or gross description. The patient is said to be well and living twenty years after an exploratory laparotomy.

A patient with a malignant abdominal neoplasm (no details given) said to be well six years after an exploratory laparotomy.

Coley (44): A carcinoma of the breast covering 150 sq. cm. which disappeared six weeks after a very severe attack of erysipelas. Nine years later there had been no recurrence. No histological examination was made in this or in any of the following cases described by Coley.

A case of sarcoma of the neck in which recession of the tumor occurred after an intentional inoculation with erysipelas. This case was observed for eight years and showed no recurrence.

A case of epithelioma of the face and cheek, in which the tumor disappeared following a violent attack of erysipelas.

A case of epithelioma of the face clinically cured two months after an attack of erysipelas, and still clinically well six months afterwards.

An epithelioma of the nose of eight years' duration, in which the tumor was absorbed after a violent attack of erysipelas. When the patient was seen several years later there was no recurrence.

Czerny (42): A carcinoma of the breast recurrent one year after operation. The recurrence was removed, a severe attack of erysipelas occurring directly afterward. This patient was observed for twenty years and there was no recurrence.

Theilhaber (43): A case of carcinoma of the breast with involvement of the pectoral muscle, the diagnosis being confirmed histologically. Shortly after the operation the axillary lymph nodes became involved, though they were not examined histologically. The involvement of the nodes disappeared after hot air treatment.

Vidal (49): Three cases of malignant growth in which recession occurred after a temperature of 40°C. He gives but the outline of one case and no details of any of the others. The author asserts that spontaneous recession was brought about in three dogs bearing sarcomata, by destroying the heat regulating center.

Czerny (42): A case of carcinoma of the uterus which was treated palliatively with curette and cautery. Five years after operation there was no clinical evidence of carcinoma.

Theilhaber and Edelberg (45): A case of carcinoma of the ovary, which could not be completely removed. At the operation, an exudate was found in the pelvis. In spite of incomplete removal the case went on to complete recovery.

Czerny (46): A sarcoma of the nose appearing after an injury and recurring after removal. The recurrence was simply curetted, and the patient has been clinically well for ten years. This tumor was probably a granuloma.

Billroth (75): A carcinoma of the breast as large as an apple which spontanously receded. The patient was free of all symptoms one year later.

Mohr (76): A tumor of the cheek which followed irritation by a ragged tooth. The growth was first noticed in 1896. It steadily increased in size and four years later gave rise to difficulty in opening the jaw. The condition was inoperable, and nothing was done save to extract the tooth. Two and a half years later the tumor had entirely disappeared. There was no histological examination.

Roux (77): A carcinoma of the stomach with many metastases scattered over the peritoneum. The primary tumor was resected; three years later the patient was alive and well.

Widmer (78): A tumor of the hand, which was clinically a carcinoma, though no microscopical examination was made; it receded spontaneously upon exposure to sunlight.

Coley (100): A round-cell sarcoma of the neck with five recurrences. An attack of erysipelas set in after the last recurrence, followed by disappearance of the tumor. No return of the tumor seven years later.

Recurrent round-cell sarcoma of the tonsil, involvement of the lymph nodes. After an attack of erysipelas the entire lesion receded.

Gerster (109): A sarcoma of the lower end of the femur. The leg was amputated and recurrence took place in the stump. An attack of erysipelas was followed by spontaneous regression of the recurrence.

Warthin and Spitzley (112): Three cases which appeared clinically to be malignant, and which receded after incomplete operation. The authors frankly doubt the validity of the cases.

Gould (122): An inoperable carcinoma of the cervix, so extensive as to result in paralysis of the lower limbs, completely receded.

A recurrent carcinoma of the breast which receded after oöphorectomy. The patient was still free ten years after operation.

Fischel (124): A perithelial sarcoma, microscopically verified, which liquefied. The fluid was evacuated by incision, the tumor remnants not being removed. Subsequently the man was clinically well.

b. Partial disappearance of malignant tumor, poorly controlled

The succeeding paragraphs give the abstracts of the cases in this group.

Hutchinson (79): A hard tumor of the breast, of thirteen years' duration, had completely receded at the time of the patient's death, though the autopsy showed innumerable visceral metastases.

Paget (80): A female of fifty-nine years had a postoperative recurrence of a mammary carcinoma. The recurrence temporarily receded when tuberculosis developed.

Billroth (81): A carcinoma of the breast of seven years' duration, which for the last two years had been gradually receding in size without ulceration, though involvement of the lymph nodes had been progressing.

Steudel (98): Subsidence of a carcinoma of the stomach after gastroenterostomy.

Lindner (99): Subsidence of a carcinoma of the stomach after gastroenterostomy.

CONCLUSIONS

TABLE 1

TYPE OF TUMOR	ORGAN INCIDENCE		ASSIGNED CAUSE OF ABSORPTION	
Carcinoma and epithelioma	Breast	28		
	Bone	4	Acute general infection	17
	Gastro intestinal tract, mouth excepted	13	Fibrosis or calcification	6
			Heat	54
			Incomplete operation	58
	Liver and gall bladder	3	Nutritional	12
	Mouth, tonsil, lip, and cheek	9	Not given	28
	Not mentioned	6		
	Skin	11		
	Testis	1		
	Urinary bladder	1		
	Uterus and appendages	82		
Chorioepithelioma	Uterus and appendages	7	Incomplete operation	6
			Acute infection	1
Endothelioma	Arm	1	Nutritional	1
	Mouth	1	Fibrosis	1
Hypernephroma	Kidney	1	Not given	
Sarcoma	Abdomen	3	Incomplete operation	5
	Axilla	1	Not given	7
	Back	1	Nutritional	2
	Bone	4	Heat	10
	Breast	2	Acute general infection	9
	Ear	1		
	Eye	1		
	Neck	3		
	Nose	1		
	Not mentioned	4		
	Skin	1		
	Tonsil	2		

Lomer's cases (100 in number) are not included in this table because they have not been given in detail in this summary. The groups in which heat is assigned as the cause of recession include cases from other groups in which fever or externally applied heat are recorded.

The statistical data to be gathered from the cases recorded in the literature are presented in the table. If all the cases are considered collectively, without regard to the probable accuracy

of the various reports, it will be noted that malignant epithelial tumors are present in the largest number, with malignant connective tissue tumors second in order of frequency. The causes of recession as given by the various authors, or as determined by the history of the case, show an almost equal number following incomplete operation and heat. Whether this heat be the result of some general acute infection such as erysipelas, tuberculosis, or pneumonia, or whether it be applied from external sources, has not been considered from the statistical standpoint.

The chief lesson to be learned from the summary of cases here presented is that occasionally, perhaps with greater frequency than is ordinarily imagined, a malignant tumor will spontaneously recede. That such a regression does ever occur suggests that there may be found some method of bringing it about at will, even though this cannot be accomplished at the present time.

The occurrence of partial or complete spontaneous recession should make one very critical in judging new therapeutic procedures, that they may not be falsely credited with the results produced by forces of the nature of which we are for the present entirely ignorant.

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EXPERIMENTAL "CARCINOMATA" OF ANIMALS AND THEIR RELATION TO TRUE MALIGNANT TUMORS

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Since Fischer (1) demonstrated a method of producing lesions of the skin of rabbits morphologically resembling human epitheliomata, reports have been published from time to time announcing the artificial production of malignant tumors by one or another procedure, the more prominent being those of Fibiger (2), Stahr (3), and Yamagiwa and Ichikawa (4).

Fibiger believes that he has produced gastric cancers in rats by feeding the animals with cockroaches, the host of the nematode worm *spiroptera*. After ingestion of the cockroach by the rat, the worms gain entrance to the tissues of the stomach, and set up in the squamous epithelium a proliferative process which may assume the appearance of a squamous carcinoma. Stahr asserts that he has caused epitheliomata of the tongue in rats by feeding the animals with oats, and Yamagiwa and Ichikawa have reported success in arousing malignant changes in the epithelium of the ear of rabbits by painting the surface repeatedly with coal-tar.

In a previous publication (5), we have shown that different varieties of epithelium react differently to the same irritant, and that the degree and extent of epithelial proliferation, the agent employed being constant, depends upon the regenerative power of the tissue and the area of the epithelial surface in contact with the irritating material. It was also pointed out that when the action of the irritant ceases there is a gradual subsidence of

the proliferation, followed by destruction and elimination of the newly formed tissue.

An analysis of the several reports mentioned reveals a number of assertions common to each, which are at variance with the recognized laws of malignant tumor growth, while, at the same time, it brings out points which cast a certain amount of doubt upon the authors' interpretation of their results.

1. For example, the age of the animal is a negligible factor in the incidence of these experimental lesions, young animals, both rats and rabbits, being almost as susceptible as old ones; hence, if we accept these tumors as malignant neoplasms, we must modify the current view concerning a "cancer age," which has hitherto been held applicable to animals as well as to man. We must conclude, in other words, that rats and rabbits differ in this respect from man, and from the mouse, in which Murray (6), Slye (7), and others have shown that age is a very important factor for the origin of carcinoma.

2. The tumors originate in tissues possessing a high grade of proliferative activity, and certain of them are restricted more or less to these tissues. Thus those described by Fibiger are confined to the large cephalic region of the rat stomach which is lined by stratified squamous epithelium; and although they invade the submucosa there is no involvement of the muscularis, and the glandular portion of the organ always remains free. The lesions described by Stahr and by Yamagiwa and Ichikawa also arise in tissues possessing a high regenerative power, the stratified squamous epithelium of the dorsum of the rat's tongue in the region of the papilla vallata, in the case of the former investigator, and the epidermis of the rabbit's ear in the case of the two latter.

3. The extent of growth depends either upon the number of foci of irritation, or upon the number of times that the extrinsic irritant has been applied and the area of the epithelial surface involved. Thus Fibiger found that the size of the gastric lesions generally depends upon the number of worms present, and the other investigators showed that the extent of proliferation depends upon the area of epithelium affected by the irritant.

4. The authors, excepting Yamagiwa and Ichikawa, who found that their lesions often increased in size after irritation had been discontinued, do not state definitely whether continuous irritation is necessary for continuous growth, and whether a type of proliferation can be inaugurated that no longer depends upon the presence of the irritant; yet it is of great importance, from a diagnostic standpoint, to know the fate of these lesions after withdrawal of the extrinsic irritant. Even Yamagiwa and Ichikawa, however, have recorded the fact that one of their assumed carcinomata "merkwürdige Weise" receded spontaneously after the discontinuation of the irritation.

5. So far as we are aware, transplantation of these lesions either is not mentioned, or is said to have been unsuccessful. Again, the presence of metastatic growths described by two of the investigators remains, after all, unproved, as the appearances pictured might be the result of chronic irritation of the lymph-nodes, or as in one of Fibiger's cuts, a heterotopic epithelial area like that sometimes seen in the peritoneal nodes of man. Furthermore, the latter author has not differentiated his pulmonary metastasis from a form of bronchopneumonia which has been described in rats, and is characterized by the presence of squamous epithelium through metaplasia of the epithelium of the bronchus. Figure 14 represents this condition, as observed by us.

The object of this paper is to place on record the results of certain of our own experiments on chronic irritation, undertaken with the view of reproducing, through means other than those employed by the various authors quoted, such lesions as they have described, in order to ascertain whether these might not be interpreted as hyper-regenerative processes rather than as true carcinomata.

In the description of our experiments upon the rat stomach (8), it will be shown that the squamous epithelium of this organ possesses a high regenerative power, and reacts to irritants in very much the same manner as does the epidermis. Although we were unable to duplicate exactly the results obtained by Fibiger, certain localized lesions were produced simulating very completely the lesions caused by the nematodes, and suggesting

the possibility of what might result from a more delicate form of irritation.

The forms of irritation employed were mechanical, chemical, and a combination of the two.[1]

Mechanical irritation was produced by balls composed of celluloid covered with spines of pig bristles, which were introduced into the normal stomach by operation, and suspended by a silk thread from the wall of the squamous region near the incision. Other balls made of cork, armed with pin points, and covered with celluloid and an outer coating of keratin for protection against the digestive action of the gastric juice, were introduced so as to lie free in the cavity of the organ; these were about the size of a pea, although a few larger ones were used. At irregular intervals of from ten to one hundred and fifty days, the animals were killed and the stomach examined. In several instances, however, the balls were removed at the end of three months and replaced by larger ones, which were allowed to remain until the death of the animals, several months later.

Since the lesions produced by these irritants showed a general similarity, varying merely in degree, only the most striking will be described.

The reaction of the squamous epithelium to spinous balls suspended from the wall consists of irregular polypoid growths situated at the site of the gastrotomy wound, the largest of which (fig. 1), measuring 2 cm. in length, was observed thirty-two days after the operation. Microscopically, the reaction is characterized by hypertrophy of the epithelium with extensive production of keratin, and some proliferation and downgrowth of epithelial cells, restricted, however, by a basement membrane and localized in the mucosa. The stomach is thrown into several large folds forming polypoid projections of the mucosa. The reaction is probably due in large part to the fact that the

[1] A total of 259 rats were used for the experiments upon the stomach and tongue. For mechanical irritation of the stomach by spinous balls, 84 rats were employed; 14 of these had the balls suspended by a silk thread, while 70 had the balls lying free in the stomach chamber. For chemical and mechanico-chemical irritation of the stomach 132 rats were necessary, while 33 animals were used in the tongue experiments and 10 for injection of the salivary glands.

gastrotomy wound was closed by a purse string suture, the suspended ball playing but a subsidiary rôle, since somewhat similar pictures were produced by simply pleating the stomach, without incision.

The lesions associated with balls lying free in the stomach are confined chiefly to the glandular portions of the organ, although papillary ulcers, generally multiple, have sometimes been observed in the squamous part (fig. 1). Such ulcers are not infrequent in the stomachs of nonoperated rats (fig. 2), and as they were not a common occurrence in the experimental animals it seems hardly permissible to attribute their presence in each case to the action of the balls, although it is not improbable that in a few cases these were the causative factor.

Histologically, the mucosa presents an irregular papillomatous structure with here and there a loss of epithelium, with or without partial or complete healing of the ulcerated area. The ulcers are generally superficial, involving only the mucosa, and are covered by bacteria, moulds, yeast, leucocytes, and epithelial squames. The epithelium shows marked hypertrophy and an overproduction of keratin, and the formation of finger-like processes of cells which extend into the mucosa, often reaching to the muscularis mucosa (fig. 3).

The general reaction of the stomach following the introduction of free spinous balls consists of an hypertrophy, most marked in the glandular region, where the walls may be 3 to 4 mm. thick; with the augmentation in thickness there occurs a great increase in the production of mucus. Multiple ulcers, both gross and microscopical, are generally still present in this region, although occasionally they have completely healed. In exceptional cases the stomach shows dilatation without compensatory hypertrophy.

When the incision made to introduce the ball involves the glandular region, the most marked lesions are noted at the site of the cut; here there occurs an irregular downgrowth of the hypertrophic epithelium which covers the area of denudation, forming cysts of varying number and size. There is considerable hypertrophy and dilatation of the tubules and an

increase in the size of the cells, particularly of those tubules lining the cavity. There is also a great increment in the number of mucous elements, with an absence or paucity of parietal cells, giving the gastric epithelium the appearance of intestine. When healing is complete, the epithelium which has grown down into the depths becomes isolated from the surface epithelium, producing a picture resembling a cystadenoma (fig. 4). In or bordering the area of injury, small areas of connective tissue of the stratum proprium are sometimes converted into osteoid tissue. The stomach walls show a varying degree of inflammation, and collections of lymphoid cells are occasionally observed in the submucosa or beneath the serosa. Small cystic dilatations of the tubules and earlike processes of mucosa projecting into the cavity of the stomach are sometimes observed in other regions of the organ. When the gastrotomy incision is confined to the squamous portion of the stomach, similar but less extensive lesions are found in the glandular region at the site or sites of injury by the ball.

The methods employed for chemical or mechanico-chemical irritation of the stomach were (*a*) direct application of an irritant to the epithelium of the stomach, and (*b*) injections of the irritant into the wall of the organ after gastrotomy. Scharlach R and pine tar, either in their original state or dissolved in oil or ether, were used as the chemical irritants, the stomachs being examined from the seventh to the fifteenth day after the infliction of the injury.

The reaction of the squamous epithelium of the viscus to cotton wicks soaked in Scharlach R oil or pine tar oil and passed through the stomach wall, resembles that of the epidermis when it is subjected to a similar form of irritation. The thickened epithelium grows along the surface of the wick to reach the outer or serous coat of the organ; while at or bordering the site where the epithelium turns outward to follow the course of the wick there is a more marked grade of hypertrophy and hyperkeratinization with atypical proliferation of the underlying cells (fig. 5). Processes of cells from the inverted epithelium reach out into the connective tissue toward similar prolongations from

the overlying epithelial layer. The stomach walls are thickened and present an inflammatory reaction.

When single pieces of rubber sponge, either impregnated with Scharlach R powder or covered with pine tar, are introduced into the stomach, they give rise to hypertrophy and proliferation of the squamous epithelium about the line of suture which closes the gastrotomy opening. The most striking reaction, observed thirteen days after the introduction of a piece of sponge impregnated with Scharlach R powder, is characterized by extreme localized hypertrophy of the epithelium with the production of thick blunt processes of cells, sometimes branching, which extend deeply into the stomach wall and reach below the normal site of the muscularis mucosa. In cross section, these processes are represented by rounded nests of cells showing central cornification. A distinct basement membrane limits these cells in their growth (fig. 6); still, though localized and restricted in its growth, the lesion bears some resemblance to an epithelioma, and may be compared with the larger lesions produced by parasites.

The results of a single injection of Scharlach R or of pine tar in oil or ether into the stomach, consist chiefly of a moderate grade of epithelial hypertrophy and the formation of epithelial cysts about the injected material.

Twice repeated injections of pine tar at intervals of seven days give rise, six days after the last injection, where the injected material comes into intimate contact with the surface epithelium, to a reaction characterized by hypertrophy of the epithelium with the production of thick processes extending below the muscularis mucosa. Here the epithelium tends to surround the injected material. There is an increase in keratin formation and an inflammatory edema of the mucosa (fig. 7). Repeated injection of the irritant may also cause papillomatous tumors, with or without ulceration, such as have already been described.

Attempts to inaugurate a proliferative process by the introduction of a rubber sponge infiltrated with Scharlach R powder, followed ten days later by the injection into this region of one or the other irritant into the wall of the stomach, result in a con-

siderable proliferation of the epithelium chiefly confined to the mucosa in the region of the suture line. Downgrowth of the epithelium about the injected material reaching below the muscularis mucosa (fig. 8) may also occur.

Injections of the irritant into the stomach wall from without the body of the rat, at the gastric edges of a gastrostomy opening, result in papillomatous tumors or ulcers showing a general resemblance to those produced by repeated injections made without opening the viscus. Owing to the impossibility of keeping rats subjected to gastrostomy alive for any considerable period (over fourteen days) the injections could not be repeated more than once.

The following conclusions may be drawn from the results of these experiments. The epithelium of the rat stomach, both squamous and glandular, possesses a high regenerative power and shows an active response to irritation. Where tissue resistance is reduced and the irritation is continued, the epithelium may invade to some depth the wall of the stomach. Lesions resembling cystadenomata may be produced in the glandular region of the stomach by simple mechanical irritation, and papillomatous tumors and lesions suggesting epitheliomata may be produced in the squamous region by chemical or mechanical means.

Now if we assume that the parasite described by Fibiger elaborates constantly an irritating secretion which acts continuously upon a wide area of epithelium, and that the epithelium responds to the stimulus by active proliferation; and if we grant the power of locomotion to the parasite, the zone of epithelial reaction is increased and new foci of irritation are produced by each progressive movement of the worm. The parasite, acting simply as a foreign body in contact with the epithelium, no doubt plays a minor part in the reaction. It thus irritates the epithelium of the stomach in a manner which we cannot duplicate; that is, by constant irritation over an ever increasing area of epithelium, upon which depends the degree and extent of epithelial proliferation in a specific tissue.

In the presence of an irritant in the tissues, atypical proliferation and invasive growth of the epithelium are in themselves doubtful criteria upon which to base a judgment of malignancy. Since marked atypical proliferation results from such relatively crude experimental methods of irritation as those described in preceding paragraphs, the more extensive reactions caused by the parasite with its refined methods are readily explainable, without malignant properties necessarily having been bestowed upon the epithelial cell.

The papillomatous tumors of the rat's tongue described by Stahr which arose after the repeated ingestion of oats, were associated with the presence of fine hairs derived from the husk of the grain; these hairs, which were incorporated in the growths, Stahr regarded as the exciting cause of the epithelial proliferation.

In our experiments upon the tongue of the rat, both mechanical and chemical irritation were employed. The mechanical method consisted of inserting into the tongue fine hairs of bearded wheat or foxglove. Several punctures were made by a needle in the dorsum of the tongue in the region of the papilla vallata, and the hairs were introduced into the openings in such a manner that the spines of the hair pointed outward, thus serving as barbs to prevent the hair from coming out. After the hairs had been thrust into the tongue for a short distance their ends were cut off close to the dorsal surface of the organ.

This form of irritation resulted in ulceration about the hairs, a considerable grade of hypertrophy of the lingual epithelium, and a downgrowth of the epithelium to surround the foreign body.

The method of chemical irritation elected was the injection into the organ, in the region of the papilla vallata, of Scharlach R dissolved in oil or ether, a hypodermic syringe with an L-shaped needle being used to inject the irritant. Little epithelial reaction followed the injection of Scharlach R in oil, owing, no doubt, to the difficulty of obtaining contact between the epithelium and the dye. However, Scharlach R dissolved in ether produced considerable ulceration, with hypertrophy and downgrowth of epithelium to wall off the area of ulceration, and meta-

plasia of the serous and mucous glands of the region involved. The gland acini were converted into squamous epithelium showing central cornification, and aggregations of these transformed gland elements presented the picture of a rather benign form of epithelioma. The stroma of the gland was edematous and showed active proliferation (fig. 9).

In order to determine whether the change in type of the gland epithelium was a true metaplasia or an extension downward into the acini of the proliferating surface epithelium of the tongue, the irritant was injected into the parotid and submaxillary glands through an incision in the skin at some distance from the site of the gland. The results of injection into these glands were even more striking than those observed in the lingual glands, and indicate that the transformation is a true metaplasia (fig. 10).

It would be wrong to conclude from these experiments that the lingual epithelium does not react to irritants to the same degree and extent as does the gastric epithelium, for technical errors, due partly to the porous nature of the tissues of the tongue, probably account for the difference. The interesting feature of the experiments is a metaplasia of the gland elements, which might be mistaken for epithelioma.

In a study of the Scharlach R reaction, we have pointed out that the reaction of the skin of rabbits caused by a single injection of the dye, reaches its height of proliferative activity about the eighth day following the injection. It was thought that if injections of Scharlach R oil were made at the same site at intervals of seven or eight days, so that one injection followed another at a time when the epithelial reaction resulting from the former injection was most active, a summation of effects might be produced. The increased difficulty of securing contact between the dye and the epithelium after the first injection was realized before undertaking the experiment.

The characteristic lesion produced in the skin of the rabbit by a single injection of Scharlach R oil consists of hyperplasia and downgrowth of the epithelium of the hair follicles, with an overproduction of keratin. In its downward course, the pro-

liferating epithelium surrounds the injected material and sends off from its periphery numerous strands of cells which extend into the depths to surround the oil droplets which they encounter, or reach out laterally into the tissues in an attempt to join similar processes from adjacent follicles. The surface epithelium may or may not participate. Cyst formation is the usual outcome of the active process.

One hundred and eight rabbits were used in this experiment, the injections being made into the skin of the buttocks or the back. These animals received from three to sixteen injections during a period of four months. In 59 rabbits the experimental area was excised and submitted to microscopical examination. In the remainder, the lesions gradually subsided and eventually disappeared clinically, though the animals were kept under observation for months after the experiment.

Three general types of reaction result from repeated injections of the dye. (*a*) When the hair follicles are chiefly involved in the proliferative process, a lesion is produced which, although often of greater degree and extent, resembles that caused by a single injection. Cyst formation is the characteristic result (fig. 11). (*b*) When the epidermis and the upper part of the hair follicles are chiefly concerned, owing to complete or partial destruction of the follicles, the lesion somewhat resembles that produced in the stomach by repeated injections of the dye. There is marked hypertrophy of the epidermis, with processes projecting from it into the connective tissue. Nests of epithelial cells showing central keratinization are observed; cysts are seldom encountered (fig. 12). (*c*) When both hair follicles and epidermis are involved, one or the other predominating, a reaction is produced which assumes the features of both (*a*) and (*b*).

In general, it may be stated that when the hair follicles assume the chief rôle in the proliferative process, cyst formation is the characteristic feature of the reaction, whereas, when the epidermis takes that part, papillary hypertrophy without cyst formation results.

A lesion worthy of separate description, since it differs from the usual type and bears a more striking resemblance to epi-

thelioma, was observed in a rabbit subjected to seven injections of the dye. The tumor, a warty growth showing a superficial area of necrosis, was removed from the animal fifty-five days after the first, and seven days after the last injection. The animal died a few days after the operation.

On microscopical examination, the hair follicles are found converted into parallel columns or strands of cells packed closely together and often anastomosing one with the other. These columns and strands are continuous above and below with large irregular columns or clumps of cells showing central cornification or beginning cyst formation. From the deeper lying clumps of cells, strands emerge to surround the oil droplets in the neighborhood. The smaller columns of cells often show a moderate grade of central keratinization. Numerous mitotic figures are observed in all parts of the lesion, which is well vascularized. The tendency of the epithelium of the hair follicles to form cysts, a characteristic of the usual reaction caused by injections of Scharlach R, is lacking or in abeyance (fig. 13). The overlying skin is ulcerated and there is a deep area of ulceration along the track of the needle. Although this lesion shows considerable deviation from the usual type, and cannot be distinguished from a true epithelioma as observed in man, we do not believe we are justified in calling it a malignant tumor. To us it appears to present only an expression of individual variation in the reaction of tissues to prolonged irritation.

Yamagiwa and Ichikawa base their claim to the production of epitheliomata on the rabbit's ear upon lesions not much more characteristic of epithelioma than the one we have just described. Although they state that they have observed epithelial cells in the blood-vessels, and metastatic deposits in the lymph-nodes, these observers by no means definitely prove their claim. The cuts of the lymph-nodes resemble the endothelial hyperplasia accompanying chronic irritation more than metastases of epithelial cells.

It is well known that benign tumors, such as chondromata, metastasize, and it is not difficult to conceive that with repeated trauma the walls of blood- or lymph-vessels may be injured,

allowing the epithelial cells to enter and be transported (as are chorionic masses) to another region of the body where they continue to grow for a time. In an unpublished experiment upon autologous grafts of proliferating ear epithelium, the proliferation being induced by single injections of Scharlach R oil, we have found such grafts surviving for fifty-five days in a foreign locality.

SUMMARY

Papillary and polypoid tumors, papillary ulcers of the squamous portion of the rat's stomach, and lesions of the glandular portion suggesting cystadenomata, are readily produced by simple mechanical injury.

Chemical or mechanico-chemical irritation of the squamous epithelium of the rat's stomach results in localized papillary tumors suggesting the cancroid growths produced by nematode worms.

The injection of Scharlach R in the region of the papilla vallata of the rat's tongue gives rise to a metaplasia of the serous and mucous glands of this region, with the production of lesions simulating a benign epithelial growth. Similar changes are produced in the parotid and submaxillary glands of rats by the same means.

Repeated injections of Scharlach R in oil into the skin of the buttocks of rabbits may cause lesions indistinguishable morphologically from human epitheliomata.

In view of the results of mechanical and chemical irritation of epithelium, as described in this paper, extreme caution should be observed before reports of the production of cancer by artificial means are accepted. In irritation tumors, atypical proliferation and invasive growth, even when extensive, are doubtful criteria upon which to base a judgment of malignancy; and in the absence of continued growth after the action of the extrinsic irritant has ceased, experimental tumors should not be classed as malignant, however close be the morphological resemblance. The fact that the lesions reported by the various observers quoted are produced as readily in young as in old animals, and

that apparently they do not possess the power of continuous growth upon transplantation into animals of the same species, increases the doubt regarding their malignant properties.

All these facts point to the conclusion already deduced from clinical observation, that age, organ specificity, and congenital defects play an important and, in many cases, a decisive rôle in the determination of the origin of cancer, and that irritation alone is an insufficient factor.

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PLATE 1

Fig. 1. Gross appearance of the polypoid ulcers produced in the squamous portion of the rat stomach by spine balls.

PLATE 1

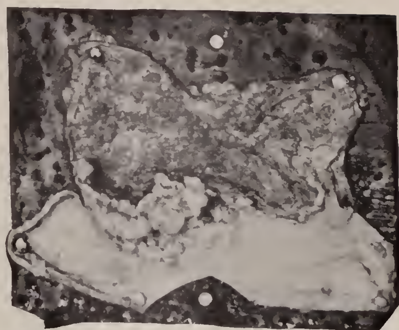


PLATE 2

Fig. 2. Spontaneous ulcers of the rat stomach, squamous portion and duodenum.

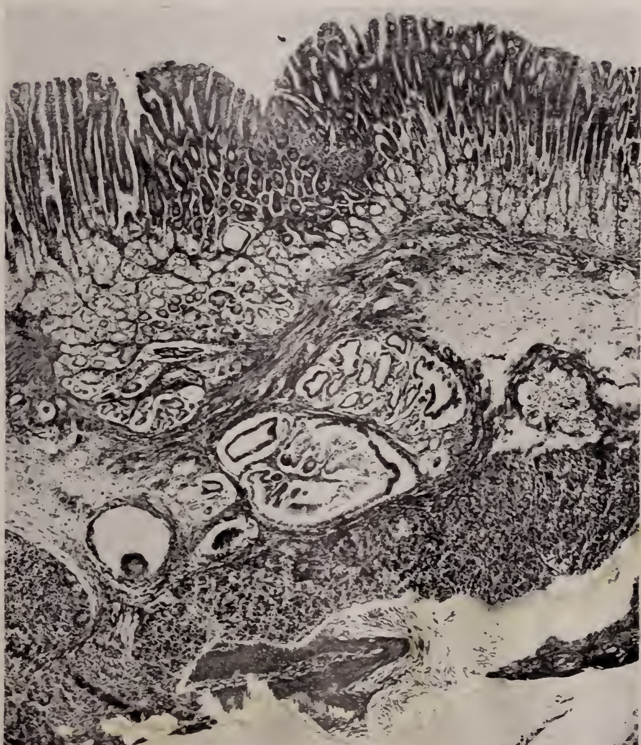
PLATE 2

PLATE 3

Fig. 3. Reaction of the rat stomach after introduction of spine ball.

PLATES 4 AND 5

Fig. 4. Healed ulcers (ulcer produced by spine ball) of stomach resembling cystadenoma, showing various types.



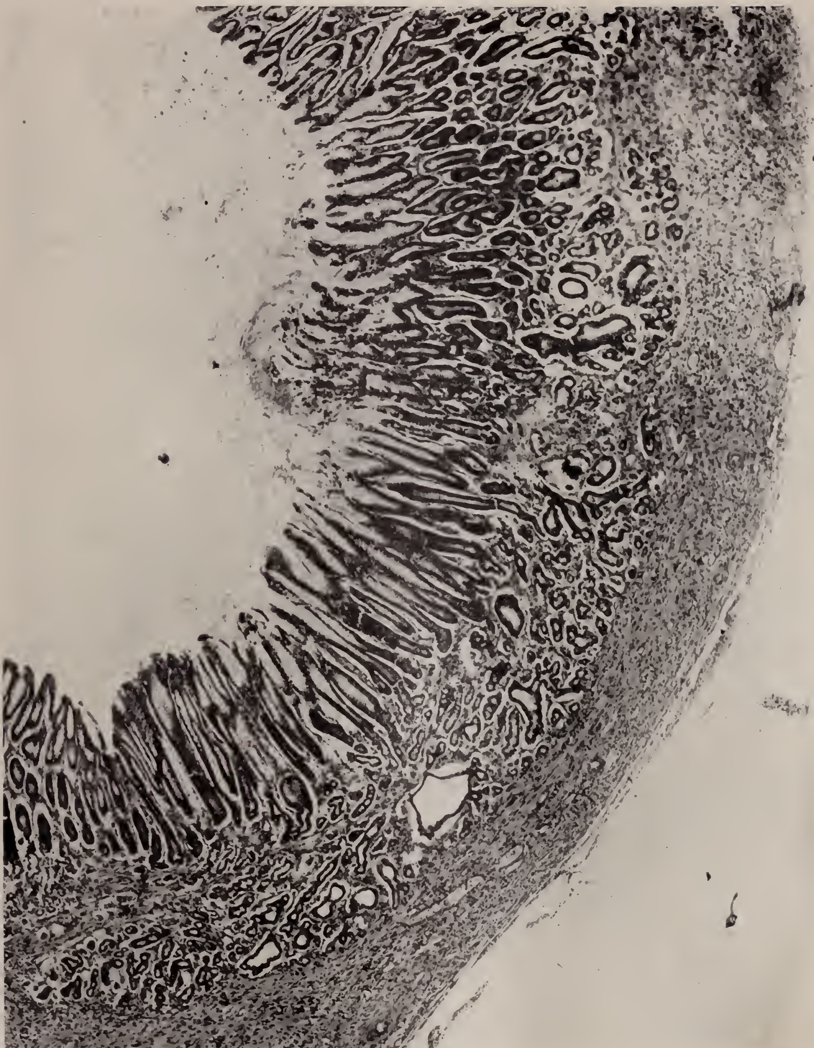


PLATE 6

Fig. 5. Marked keratinization and downgrowth of epithelium about wick.

PLATE 7

Fig. 6. Lesion produced by sponge saturated with Scharlach R powder, when introduced into the stomach of the rat.

PLATE 8

Fig. 7. Reaction of the squamous epithelium of the stomach to injections of pine tar.

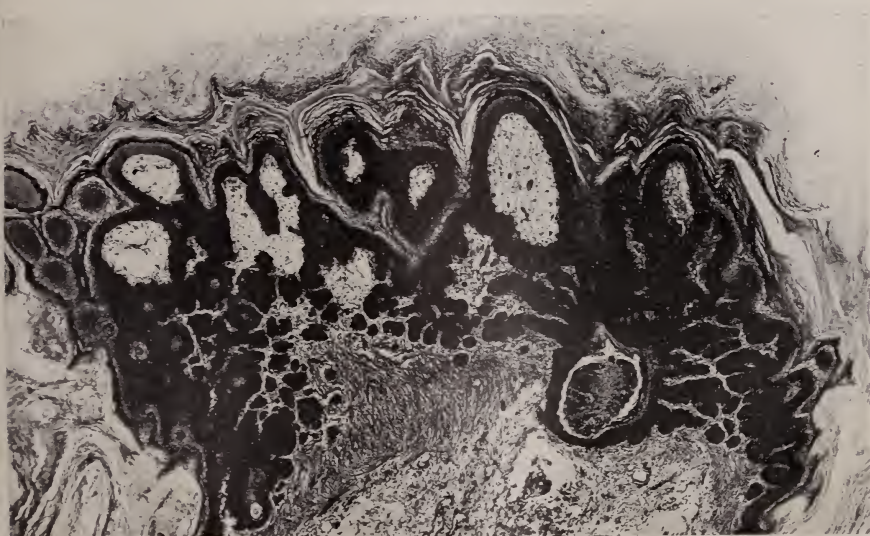


PLATE 9

Fig. 8. Downgrowth of epithelium about injected material (pine tar) following irritation with sponge saturated with Scharlach R.

PLATE 10

Fig. 9. Metaplasia of the serous glands of the rat tongue.

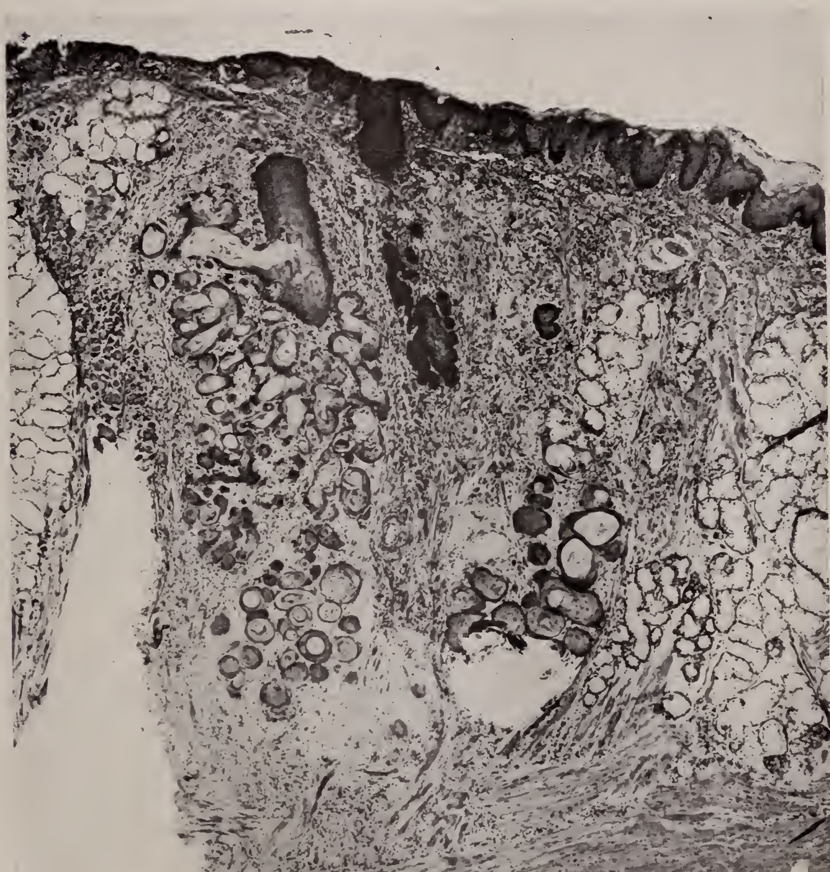
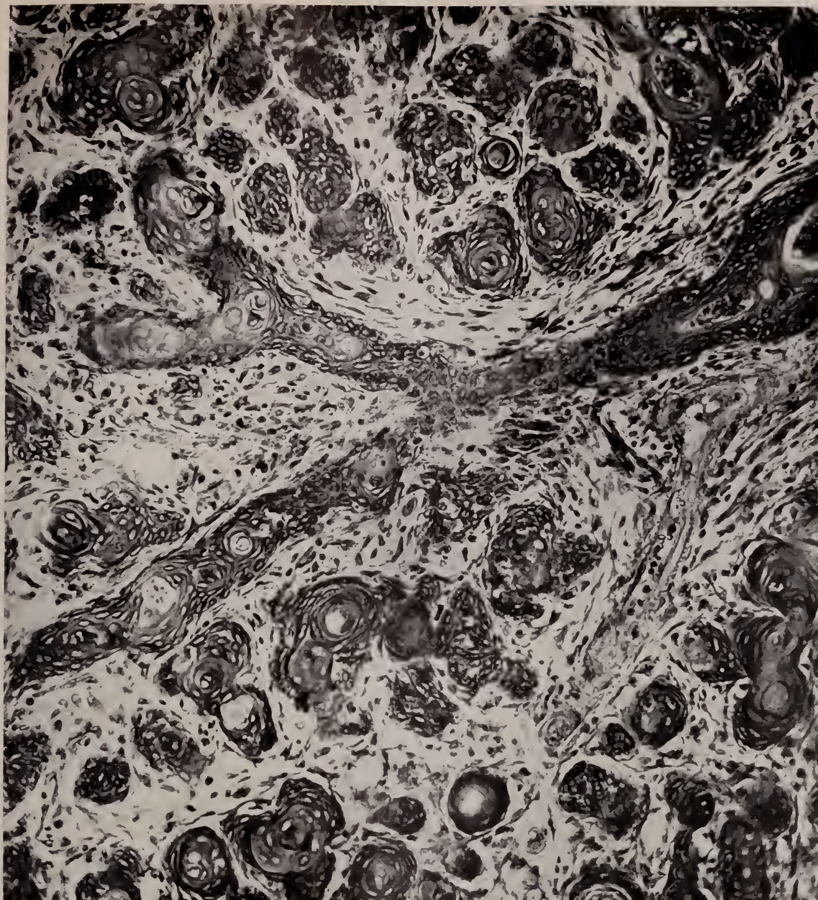


PLATE 11

Fig. 10. Different magnification of reaction in the submaxillary gland after injections of Scharlach R.



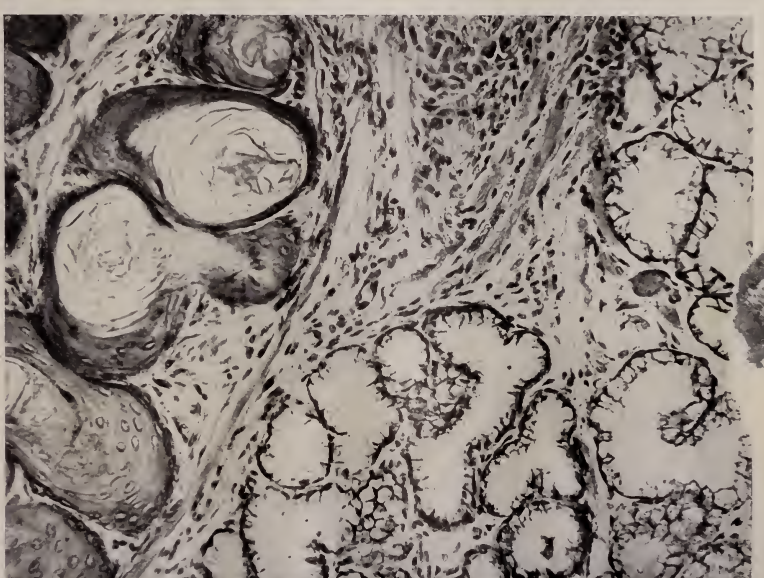


PLATE 12

Fig. 11. Type A of the Scharlach R reaction in the skin of the rabbit.

PLATE 13

Fig. 12. Type B of the Scharlach R reaction in the skin of the rabbit.

PLATE 14

Fig. 13. Unusual reaction of skin of rabbit after repeated injections of Scharlach R.

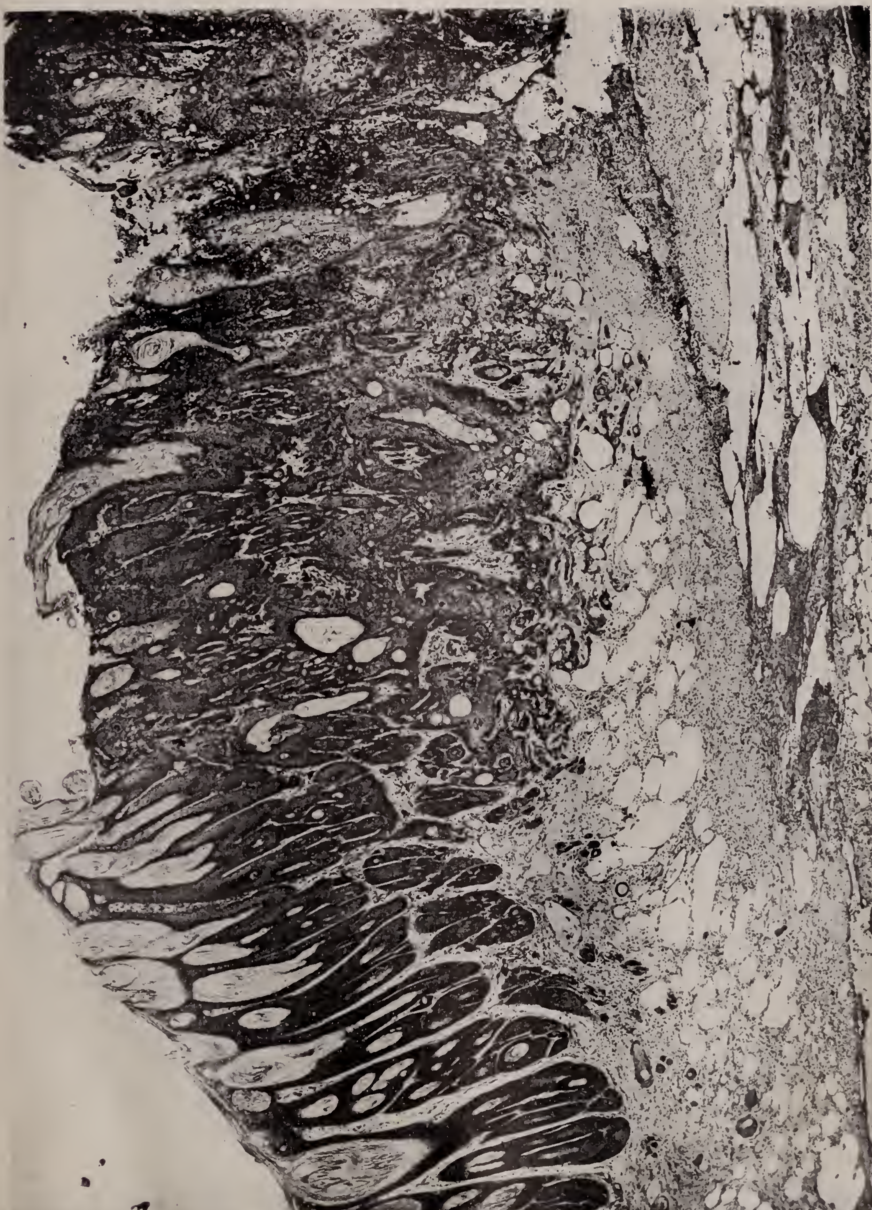
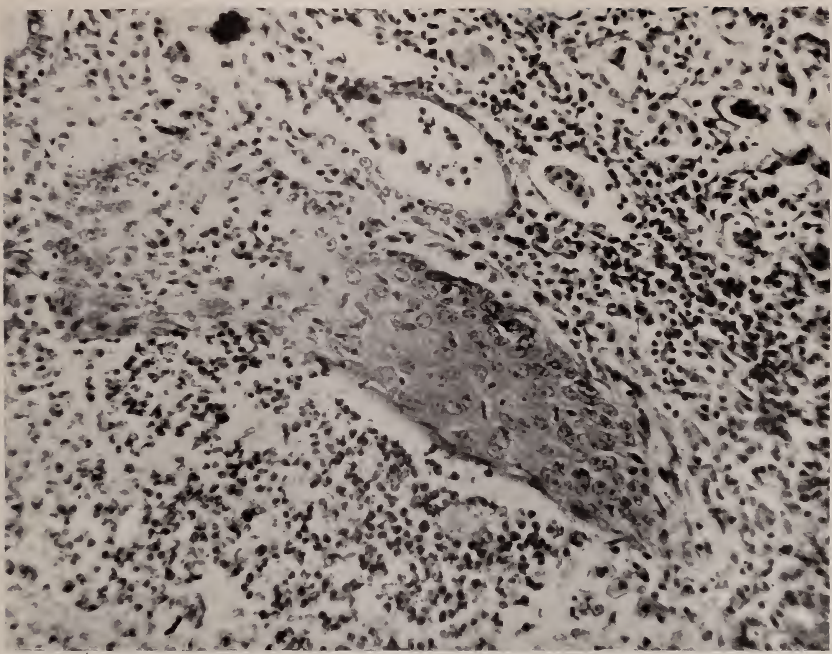
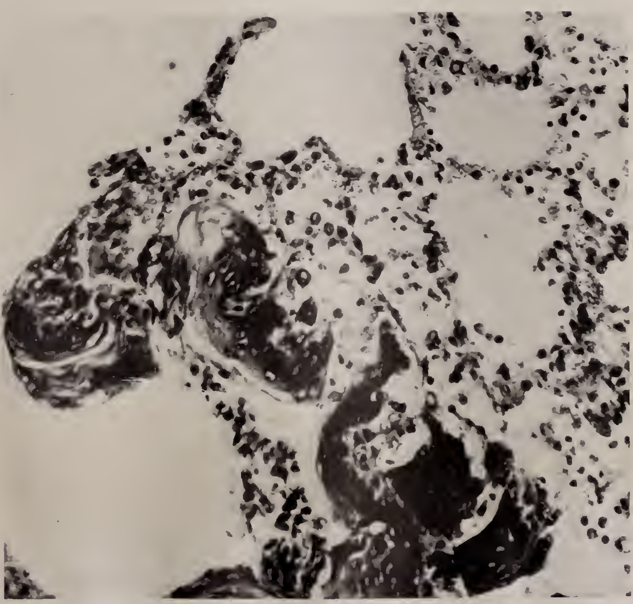


PLATE 15

Fig. 14. Metaplasia of the bronchial epithelium in the rat lung associated with bronchopneumonia. Note mitotic figures in "A."



A



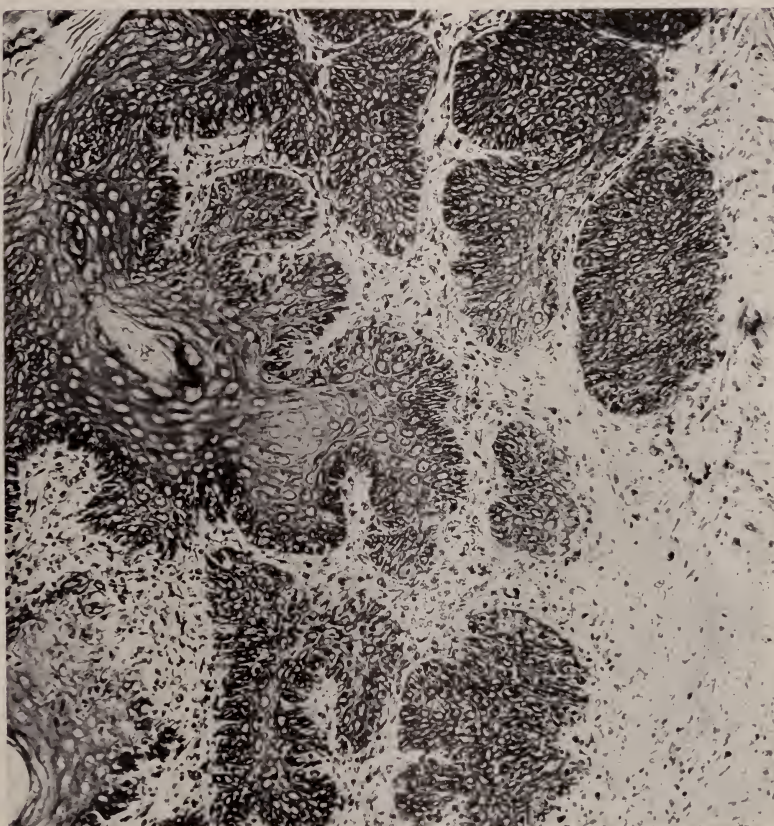
B

PLATE 16

Fig. 15. Proliferation induced in rabbit skin by parasitic skin infection. Compare with reaction induced by Scharlach R.

PLATE 17

Fig. 16. Reaction of squamous epithelium of stomach after injections of Scharlach R oil into edge of gastrostomy opening.



ADENOCARCINOMA OR ADENOMA OF THE LIVER IN A MOUSE

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From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director

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Notwithstanding the great frequency of spontaneous mammary neoplasms in the mouse, few cases of primary hepatic tumor in this species have been reported. The first example, an adenoma, probably malignant, was described by Murray (1), while Slye (2) has recorded twenty-eight cases ranging from simple benign adenoma to true carcinoma, to say nothing of several others discussed in connection with her work on the inheritability of a tendency to develop neoplasms.

The following example, which is the first that has come under observation in this laboratory, is reported on account of the comparative rarity of primary growths in this organ.

The growth (fig. 1) was discovered in a female mouse from which a spontaneous adenocarcinoma of the mamma had been removed. The animal died forty-four days later, without recurrence. At the autopsy, a nodule was found in the left lobe of the liver near the free margin, which proved upon incision to be a white lenticular mass of which the greatest diameter was about 0.5 cm. It was sharply demarcated from the remainder of the liver, which was of the ordinary color. The lungs were free from secondary growths. As decomposition was beginning, transplantation was not attempted.

Microscopically, the tumor was composed of anastomosing cords of cells resembling liver cells, except that they were very large and much more deeply stained. The nuclei, which also exceeded the normal limits, were rich in chromatin, but no mi-

totic figures were discoverable. As in the normal liver, many cells contained two or more nuclei.

The cords of these elements, though no longer disposed in the manner characteristic of the normal liver, still suggested a radial arrangement about a central vein, thus forming an irregular imitation of the lobule. Between the cords or cells there were either lumina or blood-vessels which corresponded to the nor-

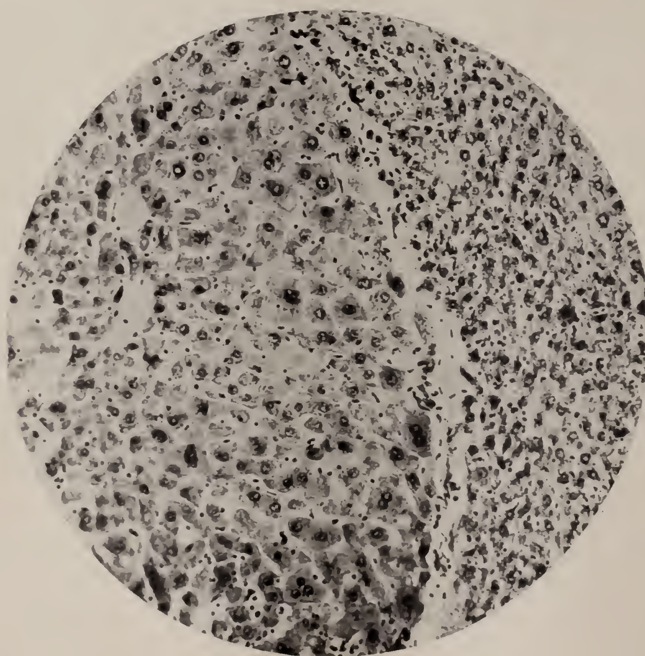

Fig. 1. Adenocarcinoma (?) of the Liver. × 200

mal capillary bile ducts and intralobular blood-vessels respectively. Even small bile ducts lined by low epithelial cells could be found, accompanied by the portal vein. In a few areas toward the center, the tumor showed a slight hemorrhage or necrosis.

The growth had no connective tissue capsule, yet invasion of the surrounding organ could not be demonstrated. About the margin, where the growth adjoined the normal liver, a few cords

of cells that had been flattened by expansive pressure formed a distinct boundary for the neoplasm. Careful study of serial sections showed that no gradual transition between the tumor and its normal surroundings, a condition which has been repeatedly observed and discussed in the human subject, could be demonstrated. On the contrary, there was the abrupt histological transition and the sharp demarcation described above. The remainder of the organ exhibited fatty changes.

The growth in question is certainly not a metastasis from a mammary carcinoma, but it is difficult to decide exactly what it is. The absence of mitotic figures, invasive growth, and metastasis, all indicate a benign neoplasm; yet, on the other hand, the abnormal size of the cells and their irregular staining, no less than the atypical arrangement, suggest malignancy. A positive diagnosis is, in fact, impossible, and the diagnosis must remain in doubt until such time as the possession of more accurate information permits a decision to be made.

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AN HEREDITARY TUMOR IN THE FRUIT FLY, DROSOPHILA

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In the fruit-fly *Drosophila melanogaster* (*ampelophila*) there have been found by various workers certain factors called "lethals," the observed effect of which is to kill the fly at some pre-adult stage. There was, however, little direct evidence to show how these factors produced their lethal effect until the discovery by C. B. Bridges of a lethal, lethal 7, which causes the development of one or several black granules within the body of the larvae (Bridges, *Genetics*, Jan., 1916). Bridges observed that in the cultures of lethal 7, about a quarter of the larvae showed these intense black "spots" and further that these larvae behaved very differently from normal larvae, frequently crawling out of the food and wandering about upon the walls of the culture bottle. These black-spotted larvae died in great numbers either upon the walls of the culture bottle or in the food. From the definite mode of occurrence of these black-spotted larvae throughout many and varied experiments made to test the mode of inheritance and the location of the factor involved in lethal 7, he concluded that these black-granuled larvae were the males having the lethal 7 factor, and that their death was probably connected with the development of the black bodies. The lethal 7 stock was turned over to the author to find out (1) the nature of the black body found in the larvae that die; (2) whether it is in itself the cause of death or only a by-product of the condition of the larvae; (3) whether by removal of the black body the life of the larva would be prolonged; (4) whether the transfer of the black body to normal larvae would cause their death; (5) the effects

of x-rays upon the black body; (6) in what tissues the black body develops.

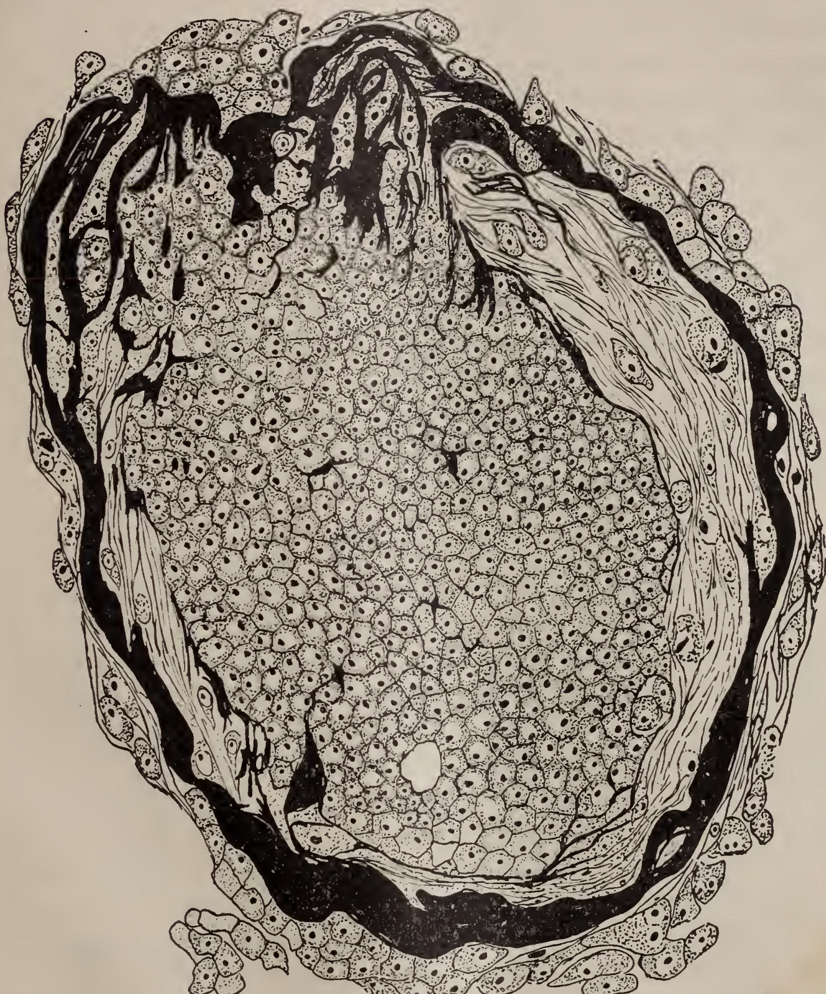
To establish the inferred causal connection between the lethal factor of this stock and the black-spotted larvae, eggs which were laid by four females from the lethal 7 stock were isolated. The larvae from these eggs were examined for spots and those with spots were removed from the culture bottle so that it might be determined whether any with spots pupated and emerged as flies, and whether the number with spots corresponded with the number of flies killed by the lethal factor. The results are shown in the first division of table 1.

TABLE 1

NUMBER OF PAIR	NUMBER OF EGGS	NUMBER OF LARVAE	NUMBER OF LARVAE WITH SPOTS	NUMBER OF FLIES	PERCENTAGE THAT HATCHED
1	174	153	38	110	63.00
2	246	219	53	151	61.00
3	129	111	30	91	70.60
4	268	223	56	111	41.3
Total.........	817	706	177	463	56.67
Control					
1	316	258	0	246	77.00
2	266	217	0	203	76.80
Total........	582	475	0	449	77.00

The total number of eggs picked out was 817, of which 706 hatched as larvae. All the larvae with spots, 177 in number, died before pupation. This number is nearly one-fourth the total number of flies and corresponds therefore to the number killed by the lethal factor. Lethal 7, like other lethals studied, is sex-linked, always killing one-half of the males. To determine whether the larvae with spots are males or not, hundreds of these have been fixed, sectioned and stained, and examined microscopically, and in every case it has been noted that the larva is a male, as should be the case if the hypothesis were correct. There is evidently the assumed causal relationship

between the lethal factor and the dark spot, because all the dark spotted larvae die, and these correspond in number to the



Text Fig. 1. Tumor Arising in Embryonic Cells Near the Posterior End of the Larva

number expected for lethal factors; and also because all the larvae with spots are males.

In the control experiment, eggs from two females that were sisters of lethal bearing females but not themselves lethal bear-

ing were isolated.[1] The results obtained are shown in the last division of table 1.

The total number of eggs picked out was 582, of which 475 hatched as larvae. Of this number, 449 emerged as flies, which is about 77 per cent of the total number of eggs laid, a normal output for this strain of flies. No larvae with spots were found and nearly all the larvae pupated and emerged as flies.

The examination of both longitudinal and cross sections of larvae with spots revealed the fact that the dark bodies are cellular growths somewhat resembling the tumors of vertebrates; they will be called tumors here in the sense that they are abnormal cellular overgrowths (text fig. 1). The cells near the center are large, polyhedral, spheroidal, or fusiform in shape. Pigment is present both within and outside the cells. Toward the periphery the cells become flattened and closely crowded together, forming laminated layers of pigment giving to the tumor the appearance of being encapsulated.

TIME OF DEATH

Just before death, the larvae with tumors become more or less restless and tend to crawl away from the food, if possible, and up the sides of the culture bottles, where they become more and more inactive and finally die. Some of these larvae in the restless stage were measured. Those of the same length were placed in the same culture bottles (table 2).

TABLE 2

LENGTH OF LARVAE	APPROXIMATE AGE OF LARVAE	NUMBER PICKED	TIME OF DEATH
mm.	*days*		
1.5–2.0	1 –1½	15	Within 15 hours
2.0–2.5	1½–2	23	Within 15 hours
2.5–3.0	2 –2½	20	Within 15 hours
3.0–3.5	2½–3	36	Within 15 hours
3.5–4.0	3 –3½	44	Within 15 hours
4.0–4.5	3½–4	32	Within 15 hours

[1] Because of linkage the white eyed females of this lethal 7 stock are known not to carry the lethal factor.

In every case it was noticed that the larvae of table 2, when placed upon food, neither bored into the food nor fed upon it. Death always occurred within twelve or fifteen hours, activity decreasing within six hours. Restlessness is apparently an evidence of oncoming death. It is also apparent that the larvae with the tumor die at varying ages. If the tumor appear quite late, i.e., not until the second or third day of the larval stage, death occurs just before pupation, i.e., about the end of the fourth day. If, on the other hand, the tumor appear on the first day, death occurs on or about the second. In many cases it has been noticed that the tumor is fully developed (i.e., has become black) in a day old larva, and that death has occurred on the second day. The tumor in the early stages of development has very little pigment and is therefore scarcely perceptible to the eye. Many larvae with light colored tumors have been isolated and it has been noticed that within twenty-four hours the tumor is quite brown in color and often before thirty-six hours it is black. The larvae recorded in table 3, varying in length from 1.5 to 4.5 mm., were without tumors. Tumors appeared in some of each of these classes within twelve hours.

TABLE 3

LENGTH OF LARVAE	NUMBER WITHOUT TUMORS	NUMBER WITH LIGHT TUMORS WITHIN TWELVE HOURS
mm.		
1.5–2.0	10	2
2.0–2.5	12	3
2.5–3.0	13	1
3.0–3.5	30	8
3.5–4.0	25	5
4.0–4.5	20	4

All the tumors were light at first appearance and became brown in color within twenty-four hours and black within thirty-six hours. Rarely does death occur until the tumor is fully developed; i.e., until the tumor is black with pigment. The tumors of the larvae of table 2 were all black in color. There is evidently a relationship between the occurrence of death and the ripening of the tumor.

To determine whether there is any relationship between the occurrence of death and the size of the tumor, larvae were picked and measured. The larvae picked out for these measurements given in table 4 were larvae that had crawled away from the food to die. The results in this table show that nearly as many deaths occur among larvae from 2 to 3 mm. in length as among those from 4 to 4.8 mm. in length. More than half the larvae measured were between 3 and 4 mm. in length, while the other half is composed of the smaller larvae from 2 to 3 mm. in length and the larger larvae from 4 to 4.8 mm. in length.

In this table are indicated also the lengths, breadths, and approximate volumes of the tumors. From these measurements were computed the correlated variates and the correlations with the probable errors, as recorded in table 5.

The correlation of the length of the larvae to the number of tumors is 0.048 ± 0.065; this is a negligible correlation. The figures on plate I bear out the same fact. The enlargement is the same for all the drawings made and one of the smallest larvae drawn contained sixteen tumors (plate I, fig. 1). The correlation of the length of larva to length of tumor is 0.127 ± 0.049; this is scarcely a significant correlation. The correlation of the length of larva to the breadth of tumor is 0.169 ± 0.048. This is likewise a correlation of doubtful significance. The correlation of length of larva and volume of tumor or of tumors, 0.094 ± 0.065, is negligible.

There is, therefore, no relation between the size of the larvae and the number of tumors, and only a doubtful relation between the size of the larvae and the size of the tumors. The correlation between the number of tumors and the length of tumors is -0.390 ± 0.042; that between the number of tumors and the breadth of tumors is -0.388 ± 0.043; that between the length of tumor and the breadth of tumor is 0.748 ± 0.022. The last three correlations are, then, all significant, and show, first, that whenever the tumors are numerous they are small, and second, that the shape of the tumors is relatively constant.

In table 6 are shown the physical constants of distribution. The mean length of the larva is 3.742 ± 0.058; its standard

TABLE 4

LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR	LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR	LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR
mm.	*mm.*	*mm.*	*cmm.*	*mm.*	*mm.*	*mm.*	*cmm.*	*mm.*	*mm.*	*mm.*	*cmm.*
1.8	0.099	0.050	0.00013		0.249	0.099			0.199	0.249	
2.0	0.099	0.086	0.00083	3.0	0.133	0.133	0.00304	3.3	0.083	0.083	0.01482
2.2	0.099	0.050	0.00013		0.099	0.099			0.249	0.249	
2.3	0.099	0.086	0.00083	3.0	0.166	0.166	0.00290	3.3	0.199	0.332	0.01147
2.3	0.249	0.166	0.00356		0.099	0.099		3.4	0.249	0.160	0.00545
2.3	0.099	0.083	0.00036	3.0	0.249	0.249	0.00102		0.160	0.160	
2.4	0.166	0.249	0.00539		0.160	0.160		3.4	0.332	0.332	0.01905
2.5	0.249	0.166	0.00356		0.330	0.033		3.4	0.332	0.249	0.01076
2.7	0.249	0.166	0.00356		0.066	0.066		3.4	0.332	0.166	0.00479
2.7	0.249	0.166	0.00356	3.0	0.083	0.083	0.00624	3.4	0.160	0.132	0.00145
	0.332	0.166			0.033	0.033		3.4	0.332	0.249	0.01076
2.7	0.083	0.083	0.00539		0.033	0.033		3.4	0.249	0.249	0.00859
	0.083	0.083		3.0	0.249	0.249	0.01616		0.099	0.099	
2.7	0.099	0.166	0.00143		0.249	0.249		3.4	0.249	0.249	0.00808
2.8	0.099	0.099	0.00080	3.0	0.132	0.199	0.01023	3.4	0.332	0.166	0.00479
	0.083	0.083			0.249	0.249		3.4	0.232	0.266	0.00884
2.8	0.249	0.200	0.00521	3.0	0.249	0.249	0.00808		0.083	0.083	
	0.249	0.249		3.1	0.249	0.166	0.00356	3.4	0.333	0.333	0.01955
2.8	0.166	0.099	0.00898	3.1	0.099	0.099	0.00051		0.083	0.083	
	0.099	0.099		3.1	0.332	0.166	0.00479	3.4	0.166	0.033	0.00036
	0.083	0.083		3.1	0.249	0.166	0.00356		0.080	0.080	
	0.249	0.166		3.2	0.160	0.099	0.00082		0.232	0.232	
	0.033	0.033		3.2	0.299	0.166	0.00356	3.4	0.166	0.166	0.02356
2.8	0.033	0.033	0.00395	3.2	0.332	0.199	0.00687		0.265	0.265	
	0.033	0.033		3.2	0.132	0.083	0.00092	3.5	0.249	0.249	0.00808
	0.033	0.033			0.132	0.083		3.5	0.050	0.050	0.00007
	0.033	0.033			0.248	0.166			0.050	0.050	
2.8	0.166	0.166	0.00287	3.2	0.166	0.099	0.00463	3.5	0.332	0.249	0.01076
	0.333	0.166			0.083	0.033			0.249	0.249	
2.8	0.199	0.166	0.00273	3.2	0.332	0.249	0.01432	3.5	0.083	0.083	0.00140
2.9	0.333	0.249	0.01575		0.249	0.166			0.083	0.083	
	0.333	0.166		3.2	0.249	0.166	0.00612	3.5	0.249	0.249	0.00808
3.0	0.333	0.249	0.01095		0.249	0.166		3.5	0.166	0.332	0.00965
3.0	0.242	0.166	0.00349	3.3	0.083	0.083	0.00029		0.365	0.249	
3.0	0.333	0.166	0.00480	3.3	0.166	0.166	0.00293		0.083	0.166	
3.0	0.333	0.166	0.00480		0.265	0.232			0.033	0.033	
3.0	0.099	0.099	0.00102		0.166	0.083		3.5	0.033	0.083	0.01359
	0.099	0.099		3.3	0.083	0.083	0.01455		0.033	0.083	
3.0	0.249	0.166	0.00386		0.083	0.083			0.033	0.083	
	0.083	0.083			0.083	0.083			0.083	0.083	

TABLE 4—*Concluded*

LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR	LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR	LENGTH OF LARVA	LENGTH OF TUMOR	BREADTH OF TUMOR	VOLUME OF TUMOR
mm.	*mm.*	*mm.*	*cmm.*	*mm.*	*mm.*	*mm.*	*cmm.*	*mm.*	*mm.*	*mm.*	*cmm.*
3.5	0.332	0.332	0.01905	4.0	0.166	0.099	0.00085	4.4	0.199	0.083	0.00413
3.5	0.332	0.332	0.01905	4.0	0.249	0.249	0.00808		0.166	0.199	
3.5	0.249	0.249	0.01616	4.0	0.332	0.332	0.01905	4.4	0.249	0.332	0.01436
	0.249	0.249		4.0	0.166	0.083	0.00590	4.4	0.166	0,166	0.00239
3.6	0.415	0.249	0.01315	4.0	0.166	0.332	0.00955	4.4	0.332	0.332	0.02725
3.6	0.498	0.415	0.04485	4.0	0.332	0.249	0.01076		0.332	0.083	
3.7	0.249	0.249	0.00808	4.0	0.166	0.166	0.00239		0.249	0.083	
3.7	0.332	0.332	0.01905	4.0	0.249	0.249	0.01346		0.249	0.249	
3.7	0.332	0.249	0.01076		0.166	0.249			0.0332	0.0332	
3.7	0.664	0.332	0.03832	4.0	0.166	0.166	0.00290		0.0332	0.0332	
3.7	0.332	0.242	0.01020		0.099	0.099			0.0332	0.0332	
	0.050	0.050		4.0	0.099	0.099	0.00197		0.0332	0.0332	
3.7	0.160	0.332	0.00984		0.066	0.066			0.0332	0.0332	
	0.160	0.080		4.1	0.415	0.332	0.02375	4.5	0.332	0.332	0.01905
3.7	0.332	0.249	0.01142	4.1	0.166	0.083	0.00598	4.5	0.249	0.249	0.00838
	0.083	0.083		4.1	0.415	0.249	0.01355		0.083	0.083	
	0.166	0.066			0.083	0.083		4.6	0.332	0.166	0.00479
3.7	0.332	0.249	0.01076	4.3	0.249	0.166	0.00697	4.6	0.099	0.099	0.00051
3.8	0.418	0.166	0.00602		0.099	0.099		4.6	0.332	0.166	0.00479
3.9	0.166	0.166	0.00762		0.099	0.099					
	0.366	0.166			0.166	0.166					

deviation, 1.154 ± 0.041. The mean length of the tumor is 0.488 ± 0.011; its standard deviation, 0.217 ± 0.008. The mean breadth of the tumor is 0.362 ± 0.009; its standard deviation, 0.174 ± 0.006. The mean number of tumors is 2.723 ± 0.135; its standard deviation, 2.696 ± 0.096. The mean volume of tumors is 0.008 ± 0.0005; its standard deviation, 0.008 ± 0.0004.

There seems to be no definite relationship between the size of the tumor or the number of tumors and the time of the occurrence of death. The smallest tumor may appear in the largest larva and still cause death. There is, however, a relationship between the occurrence of death and the stage of development of the tumor, as already stated. Death may occur at any period of the larval life, and depends upon a definite stage in the development of the tumor. The lethal factor 7 evidently manifests itself in the form of this lethal tumor.

TABLE 5

CORRELATED VARIATES	CORRELATION	PROBABLE ERROR
Length of larva to number of tumors	0.048	±0.065
Length of larva to length of tumors	0.127	±0.049
Length of larva to breadth of tumors	0.169	±0.048
Length of larva to volume of tumors	0.094	±0.065
Number of tumors to length of tumors	−0.390	±0.042
Number of tumors to breadth of tumors	−0.388	±0.043
Length of tumors to breadth of tumors	0.748	±0,022

TABLE 6

Physical constants of distribution

	MEAN	PROBABLE ERROR	STANDARD DEVIATION	PROBABLE ERROR
Length of larva	3.742	±0.058	1.154	±0.041
Length of tumor	0.488	±0.011	0.217	±0.008
Volume of tumor	0.008	±0.0005	0.008	±0.0004
Breadth of tumor	0.362	±0.009	0.174	±0.006
Number of tumors	2.723	±0.135	2.696	±0.096

THE SEX-LINKED INHERITANCE OF THE TUMOR

The linkage experiments of C. B. Bridges showed that the lethal 7 factor which produces the tumor, and thereby the death of the fly, is sex-linked in inheritance, being located in the X-chromosome (at the locus 0.01).

The X-chromosome, of which the female has two, carries the factor for sex. After the process of maturation in the female, there is one X-chromosome left in each egg, while after a similar process in the male, one half the spermatozoa receive the X-chromosome and the other half its mate, the Y-chromosome. If an X-bearing spermatozoon should fertilize an egg the result will be an XX individual or female. If a Y-bearing spermatozoon should fertilize an egg, the result will be an XY individual, or male. Since the two kinds of spermatozoa appear in equal numbers, males and females are produced in equal numbers. In stocks of flies having lethal factors, however, only half as many males as females appear. Since the recessive lethal factor is present in only one of the two X-chromosomes, one-half of

the males from a lethal bearing mother will get the X-chromosome that carries the lethal factor, and such males will perish. The other half of the males will get the X-chromosome that carries the normal allelomorph of the lethal factor and such males will live. None of the females die, because those that contain the lethal bearing X-chromosome have received also from the father another chromosome with the dominant normal allelomorph of the lethal factor. Therefore since the tumor of lethal 7 has the same inheritance as its lethal factor, the females of that stock do not develop tumors. To produce a female with a tumor, it would be necessary that each parent contain an X-chromosome with a factor for the lethal which is the cause of the tumor; but it is not possible to produce such a female, since all males with tumors die. The tumor is sex-linked in inheritance because the factor for the tumor is contained in, and transmitted by, the X-chromosome. It follows, in fact, the regular order of transmission shown by all sex-linked characters.

POSITION OF TUMOR IN LARVA

Larvae with tumors were selected from cultures A, B, and C. These were etherized just enough to make them quiet while measurements were made of the length of the larvae and of the lengths and breadths of the tumors. The location of the tumors was also noted. They may be found in any segment of the body, as noted in table 7. By plotting the results indicated in table 7, a bimodal curve is obtained (text fig. 2). Though the tumor may occur in any segment, it occurs more often in segments twelve and six.

The figures on plate I are camera lucida drawings of larvae with tumors, showing that the tumor may occur in any segment and that more than one tumor may occur.

REMOVAL OF TUMORS BY OPERATION

Larvae with tumors were washed in sterile water by transferring the larvae from one watch glass with sterile water to another, making the transfer five or six times; then placed upon

moist sterile absorbing paper in a watch glass to be etherized. Care in administering the ether must be exercised, as too much ether will cause the larvae to contract violently, making them

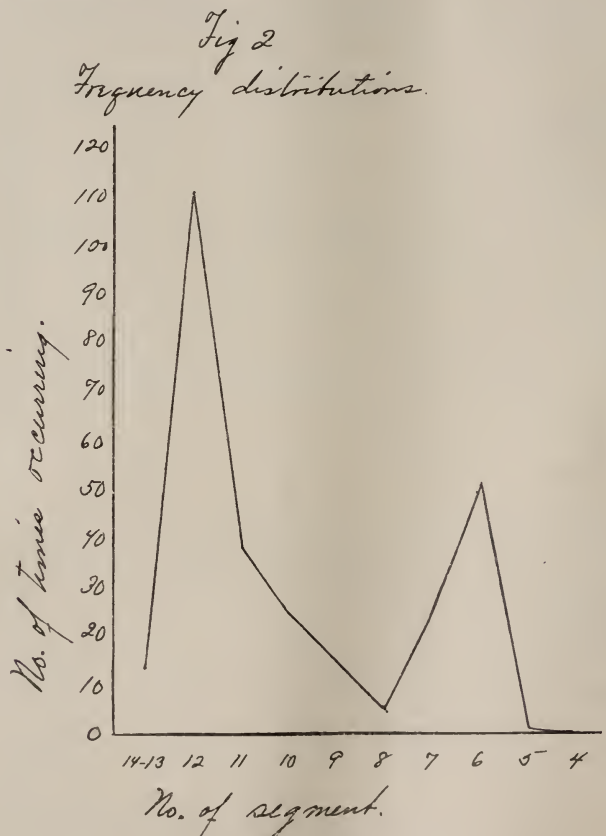
TABLE 7

POSITION OF TUMORS IN SEGMENTS	OCCURRENCES IN CULTURE A	OCCURRENCES IN CULTURE B	OCCURRENCES IN CULTURE C	TOTAL
14–13	5 (5)*	(6)	(2)	(13)
14–13–12	1	2		
14–13–12–11		1		
14–13–12–10		2	1	
14–13–11			1	
14–13–12–11–10		1		
12	11 (22)	26 (55)	20 (34)	(111)
12–11	2	6	4	
12–10	4	1	2	
12–9		6	1	
12–8	1		1	
12–7		6	1	
12–6			2	
12–10–9	3	1		
12–9–7			1	
12–11–10–6			1	
12–7–6			1	
12–11–9		1		
11	9 (11)	5 (15)	4 (12)	(38)
11–9–8		1		
11–8–7			1	
11–7–3			1	
10	4 (12)	4 (9)	(4)	(25)
10–7	1			
9	1 (4)	1 (10)	(2)	(16)
8	1 (3)	(1)	(2)	(6)
8–5	1			
7	4 (5)	5 (11)	4 (9)	(25)
6	12 (12)	16 (16)	10 (13)	(51)
5	(1)			(1)
				(286)

* The numbers in parenthesis indicate the total number of times the tumor has occurred in a given segment.

useless for the operation. When the larvae were quiet and relaxed, they were placed under the binocular. A minute cut was made through the body wall above the tumor with a pair of

iridectomy scissors. Slight pressure was then applied to the body wall to force the tumor out of the incision. The tumor was often forced out by internal pressure as soon as the cut was made. If the cut was the least bit too large, most of the intestine would be forced out also.



TEXT FIG. 2

Larvae with only one tumor were operated upon. The number of tumors removed successfully was about sixteen hundred (1600). About 5 per cent of the larvae from which tumors were removed lived twenty-four hours after the operation. The wound would often be closed within twelve hours. Not any of these larvae pupated. As a control, fourteen hundred nor-

mal larvae were operated upon, a minute cut being made through the body wall. Of these, about 5 per cent recovered from the operation; these afterward pupated and emerged as normal flies. Since only a small percentage of these controls survived the operation, it is possible that the death of the majority of the larvae from which the tumors were removed might likewise have been due to the shock of the operation, but on the other hand, the small percentage (the same as that of the control, however) that survived the operation and lived for fifteen hours and more may have died from the injurious effects that had already been produced by the tumor. That the operation was of beneficial effect upon the larvae having tumors can scarcely be doubted in view of the fact that unoperated larvae seldom survive so long as the operated, which in as large numbers as 5 per cent successfully passed the first stage of recovery, though they ultimately succumbed.

Tumors were also removed, about fourteen hundred in number, and inserted into as many normal larvae. As a control, sterile charcoal was inserted into normal larvae. A cut was made through the body wall of the normal larvae, and the tumor (or charcoal) was then pushed into the body cavity with a small arrowshaped blade. Insertion of the piece of charcoal was as difficult as that of the tumor, if not more difficult, because the charcoal was more easily forced out again by internal pressure; thus the procedure often had to be repeated several times, and the piece forced further into the body cavity. The tumor, on the other hand, moist with blood, would adhere more readily. Nearly 5 per cent of the larvae into which fragments of charcoal were inserted survived the operation, pupated, and emerged as normal flies; in many of these, particles of charcoal were present in the abdominal cavity of the fly, while in other cases they were left behind in the pupa case. The death of most of the larvae, 95 per cent, into which tumors were inserted, was in all probability due to the shock of the operation, as shown by the controls, while the death before pupation of the remaining 5 per cent must have been due to the inserted material.

Tumors were ground in Locke's solution with all necessary aseptic precautions, and a small portion of the mixture was forced into the body cavity of normal larvae with a capillary pipette. Out of one hundred larvae thus operated upon, forty survived the operation; i.e., the wound was healed and the larvae were active and feeding two hours after the operation. Although no visible tumor developed, none of these pupated, death occurring within twelve hours. As a control to this experiment, an equal number of larvae were pierced with capillary pipettes; into half of these was forced a small amount of Locke's solution. Fifty per cent of those pierced with the pipette, without any injection, survived the operation, pupated, and emerged as normal flies. Of those into which was forced the Locke's solution, nearly 40 per cent survived, pupated, and became flies. It is evident that the tumor cell suspension produces a toxic effect upon the larvae.

THE INFLUENCE OF x-RAYS UPON THE TUMOR

The following experiments were performed in coöperation with Dr. J. L. Kantor, who offered the use of his apparatus for this purpose. The current used was generated by an interrupterless transformer. The larvae and pupae to be exposed were placed upon a glass plate 30 cm. from the anode. The rays were filtered through 1 mm. aluminum. The amount of current used in each of the following experiments was 6 milliamperes, the Coolidge tube "backing up" to a 4-inch spark gap.

Larvae with tumors, when exposed every day for eight fifteen-second periods interrupted by five-second periods of rest, lived from six to fifteen hours longer than larvae of the same length not exposed to x-rays, as shown in table 8.

The normal larvae exposed to the same dose of x-rays showed a tendency to pupate earlier than those not exposed. This early pupation was not due to drying, as the absorbing paper upon which the larvae rested was kept moist.

All the eggs, larvae, and pupae from five pairs of flies were exposed to x-rays every day until the new generation emerged from the pupae. The results, shown in table 9, do not indicate

any effect upon the development of the tumor as the ratio of twice as many females as males remains the same, the larvae with tumors dying as before. The only difference noted was the

TABLE 8

LARVAE WITH TUMORS	NORMAL LARVAE	DURATION OF EACH EXPOSURE	NUMBER OF DAYS EXPOSED	DATE OF FIRST EXPOSURE	TIME OF DEATH OF LARVAE WITH TUMORS	PUPATION OF NORMAL LARVAE
20	20	Eight 5-second periods interrupted by 5-second periods of rest	4	July 12, 1916	2 July 25 7 July 26 3 July 27 8 July 28	5 July 25 15 July 26
10	10	Eight 5-second periods interrupted by 5-second periods of rest	3	July 25, 1916	3 July 27 7 July 28	4 July 26 6 July 27
10	10	Eight 5-second periods interrupted by 5-second periods of rest	3	July 27, 1916	5 July 29 5 July 30	3 July 28 7 July 29
10	10	Eight 5-second periods interrupted by 5-second periods of rest	3	July 28, 1916	3 July 29 7 July 30	4 July 30 6 July 31
10	*Control* 10	0	0	*Date picked* July 25, 1916	3 July 25 7 July 26	4 July 27 6 July 28

emergence of the flies exposed to x-rays twenty-four to thirty-six hours earlier than in the control experiments.

The eggs, larvae, and pupae of four pairs of flies from pair II of table 9 were also exposed to x-rays every day. A similar treatment was given to all the offspring of two pairs of flies from II.3 (table 10). Three generations of flies were thus exposed

daily to x-rays from the egg stage of the first generation to the adult stage of the third generation. The results in table 9 indicate no effect upon the larvae with tumors.

TABLE 9

First generation

NUMBER OF PAIR	DURATION OF EXPOSURE	NUMBER OF DAYS EXPOSED	DATE OF PAIRING AND FIRST EXPOSURE	DATE OF APPEARANCE OF OFFSPRING	TOTAL OUTPUT	
					R♀sW	R♂sW
I	Eight 15-second periods interrupted by 5-second periods of rest	22	July 27, 1916	August 6, 1916	72–66	1–69
II	Eight 15-second periods interrupted by 5-second periods of rest	22	July 27, 1916	August 6, 1916	55–37	0–49
III	Eight 15-second periods interrupted by 5-second periods of rest	21	July 28, 1916	August 7, 1916	45–36	0–47
IV	Eight 15-second periods interrupted by 5-second periods of rest	21	July 28, 1916	August 7, 1916	63–65	2–57
V	Eight 15-second periods interrupted by 5-second periods of rest	21	July 29, 1916	August 8, 1916	54–42	2–49
Control			*Paired*			
I	0	0	July 27, 1916	August 9, 1916	59–44	0–35
II	0	0	July 28, 1916	August 11, 1916	57–40	1–36

Larvae operated upon were also exposed to x-rays. The results in table 11 show that larvae with tumors removed, when exposed to x-rays, live from six to twelve hours longer than the controls or larvae with tumors removed but not exposed to x-rays. Similar results are obtained when normal larvae into

which tumors have been inserted are exposed to x-rays, as indicated in table 12.

TABLE 10

Second and third generation

NUMBER OF PAIR	DURATION OF EXPOSURE	NUMBER OF DAYS EXPOSED	DATE OF PAIRING AND FIRST EXPOSURE	DATE OF APPEARANCE OF OFFSPRING	TOTAL OUTPUT	
					R♀sW	R♂sW
II 1	Eight 15-second periods interrupted by 5-second periods of rest	25	August 11, 1916	August 19, 1916	42–44	1–48
II 2	Eight 15-second periods interrupted by 5-second periods of rest	25	August 11, 1916	August 21, 1916	45–41	0–46
II 3	Eight 15-second periods interrupted by 5-second periods of rest	25	August 11, 1916	August 20, 1916	54–59	0–53
II 4	Eight 15-second periods interrupted by 5-second periods of rest	25	August 11, 1916	August 20, 1916	57–48	1–51
II 3–1	Eight 15-second periods interrupted by 5-second periods of rest	16	August 20, 1916	August 29, 1916	48–54	1–37
II 3–2	Eight 15-second periods interrupted by 5-second periods of rest	16	August 20, 1916	August 28, 1916	37–34	0–27
Control	0	0	*Paired* August 11, 1916	August 22, 1916	43–45	0–39

Of the normal larvae operated upon as a control to the experiment in which tumors were removed and inserted, one hundred were exposed to x-rays. Table 13 shows a slight increase in the

TABLE 11

LARVAE WITH TUMORS REMOVED	DURATION OF EXPOSURE	DATE OF OPERATION AND FIRST EXPOSURE	NUMBER OF DAYS EXPOSED	HEALING OF WOUND	OCCURRENCE OF DEATH
	minutes				
10	2	August 28, 1916, 4.30 p.m.	2	Before 12 hours	2 before 24 hours; 8 after
10	0	Operation August 28, 1916	0	After 12 hours	All before 24 hours
10	2	August 29, 1916, 4.30 p.m.	2	Before 10 hours	3 before 24 hours; 7 after
10	0	Operation August 29, 1916	0	After 12 hours	All before 24 hours
10	2	August 30, 1916, 4.30 p.m.	2	Before 10 hours	4 before 24 hours; 6 after
10	0	Operation August 30, 1916	0	After 12 hours	All before 24 hours
10	2	August 31, 1916, 4.30 p.m.	2	Before 10 hours	2 before 24 hours; 8 after
10	0	Operation August 31, 1916	0	After 12 hours	All before 24 hours
10	2	September 5, 1916, 4.30 p.m.	2	Before 10 hours	3 before 24 hours; 7 after
10	0	Operation September 5, 1916	0	After 12 hours	All before 24 hours

TABLE 12

LARVAE WITH TUMORS INSERTED	DURATION OF EXPOSURE	DATE OF OPERATION AND FIRST EXPOSURE	NUMBER OF DAYS EXPOSED	HEALING OF WOUND	OCCURRENCE OF DEATH
	minutes				
10	2	August 29, 1916, 4.30 p.m.	2	Before 10 hours	3 before 24 hours; 7 after
10	0	Operation August 29, 1916	0	After 12 hours	All before 24 hours
10	2	August 30, 1916, 4.30 p.m.	2	Before 10 hours	4 before 24 hours; 6 after
10	0	Operation August 30, 1916	0	After 12 hours	All before 24 hours
10	2	September 6, 1916, 4.30 p.m.	2	Before 10 hours	2 before 24 hours; 8 after
10	0	Operation September 6, 1916	0	After 12 hours	All before 24 hours
10	2	September 7, 1916, 4.30 p.m.	2	Before 10 hours	3 before 24 hours; 7 after
10	0	Operation September 7, 1916	0	After 12 hours	All before 24 hours
10	2	September 8, 1916, 4.30 p.m.	2	Before 10 hours	5 before 24 hours; 5 after
10	0	Operation September 8, 1916	0	After 12 hours	All before 24 hours

TABLE 13

NORMAL LARVAE	DURATION OF EXPOSURE	DATE OF OPERATION AND FIRST EXPOSURE	NUMBER OF DAYS EXPOSED	HEALING OF WOUND	NUMBER OF FLIES THAT EMERGED
	minutes				
20	2	August 30, 1916, 4.30 p.m.	2	Before 10 hours	1
20	0	Operation August 30, 1916	0	After 10 hours	0
20	2	September 5, 1916, 4.30 p.m.	2	Before 10 hours	0
20	0	Operation September 5, 1916	0	After 10 hours	1
20	2	September 6, 1916, 4.30 p.m.	2	Before 10 hours	2
20	0	Operation September 6, 1916	0	After 10 hours	1
20	2	September 7, 1916, 4.30 p.m.	2	Before 10 hours	2
20	0	Operation September 7, 1916	0	After 10 hours	1
20	2	September 8, 1916, 4.30 p.m.	2	Before 10 hours	1
20	0	Operation September 8, 1916	0	After 10 hours	1

percentage of the number of larvae surviving the operation, as compared with that of the number of normal larvae operated upon but not exposed to x-rays.

In the x-ray experiments, there is no indication that the x-rays had any obvious effect upon the tumor. It developed and remained as lethal as ever in all the flies exposed, even when the exposure was repeated each day continuously through the entire life cycle of three generations of flies. More definite conclusions cannot be drawn, however, until the experiment has been repeated using varying doses of the x-rays. It may be that the rays, in the dose used, were not of a strength appropriate to affect the tumors.

There was a decided influence upon the rate of healing of the wound. It is possible that the rays had a tendency to decrease infection, thus increasing the rate of healing and prolonging the life of the larvae

DEVELOPMENT OF THE TUMOR

The tumor may take its origin in various regions of the body of the larva. It may develop in the ganglion of the proventriculus, located between the brain and the proventriculus. When the tumor develops in this region, the salivary glands usually become affected since they are innervated by this ganglion (see fig. 5, plate I).

The tumor may develop in groups of embryonic cells or imaginal rudiments located in the dorsal region of the thoracic segments and near the posterior end of the abdomen. The tumor shown in text figure 1 took its origin in an aggregation of embryonic cells near the posterior end.

In the early stages of the development of the tumor there is first a deposit of pigment, followed by a rapid proliferation of the cells which, as development goes on, push the older cells filled with pigment toward the periphery and there form the laminated layers of pigment with the flattened peripheral cells shown in text figure 1.

SUMMARY

1. A sex-linked factor in a stock of Drosophila called lethal 7 manifests itself in the form of a lethal tumor in the sense defined on page 282.

2. The time at which death takes place depends upon the stage of development of the tumor.

3. Five per cent of the sixteen hundred larvae from which tumors were removed survived the operation and lived longer than they would have done without the operation. All of these died before pupation, death being probably due to injurious effects already induced by the tumor before its removal.

4. Four per cent of fourteen hundred normal larvae into which tumors were inserted survived the operation, but died before pupation. Forty per cent of one hundred normal larvae into which tumor cell suspension was injected survived the operation but died later. The occurrence of death before pupation was probably due to the injected material.

5. There is no obvious effect upon the tumor when larvae containing it are exposed to x-rays.

6. The tumor may develop in the proventriculus ganglion, or in the salivary glands, or in the imaginal rudiments of the thorax and abdomen.

7. The tumor is epithelial in structure, and pigment producing.

In conclusion, I wish to acknowledge my indebtedness to Prof. T. H. Morgan for his interest in the progress of my work and for his many valuable suggestions, as well as to Dr. C. B. Bridges for the lethal 7 stock which has enabled me to do this work.

PLATE 1

EXPLANATION OF FIGURES

All the drawings were made with camera lucida, 16 mm. objective and 6 × ocular.

Fig. 1. Dorsal view of the anterior (above) and posterior (below) portions of a larva with sixteen tumors.

Fig. 2. Ventral view of the anterior end of a larva with a tumor at the end of each salivary gland.

Fig. 3. Ventral view of the posterior end of a larva with three tumors.

Fig. 4. Ventral view of the anterior portion of a larva with tumors in the proventricular ganglion and the salivary glands.

Fig. 5. Lateral view of a larva with one large tumor in segments 8–9 and the left salivary gland entirely impregnated with pigment.

Fig. 6. Dorsal view of the last three segments of a larva with three tumors.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THE BIOLOGICAL TREATMENT OF CANCER[1]

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ANTIPARASITIC METHODS

It is the purpose of this paper to review critically some of the methods and results of the past two decades in cancer research, a branch of pathology which has not failed to share in the general progress of medicine. During this period innumerable experiments have been performed, and the most diverse materials employed, in an endeavor to solve the problem of the cure of cancer.

Thus Bra has employed cultures of *Nectria ditissima*, a parasitic myxomycete occurring in certain plants, and causing a disease resembling cancer in man. Cultures heated to 120° and filtered cause a febrile reaction in cancerous patients which is not found in healthy persons.

Mongour and Gentes, employing this method, found that while the pain, the hemorrhage, and the discharge ceased, cure did not take place, and a similar result has been recorded by Parlavecchio.

Bra later prepared an anticancerous vaccine from a parasite similar to that of plants, but obtained from human tumors. This vaccine, according to Silva and Vidal, caused a febrile reaction but no cures.

Schmidt stated that *Mucor racemosus* is the causative agent of cancer, and that preparations of its cultures exert a therapeutic effect in cancer patients. He published the statement that he

[1] The Editor wishes to thank Dr. Karl M. Vogel for his kindness in translating this article from the Italian.

The author has not read the proof.

had succeeded in increasing its virulence in rats to such a point that in successive inoculations up to the eighth generation he finally achieved 100 per cent of results in 8 rats, although in the first 40 animals tumors had developed in but 2 cases. Furthermore, treatment with dead cultures from tumors obtained in this way gave 20 to 25 per cent of cures.

In view of the negative results of Schuberg, Baisch, and von Dungern and Werner, these experiments may be regarded as quite without value.

Nevertheless, Schmidt and others have reported clinical cases of neoplasm cured by means of cancroin or antimeristem; thus Claes recorded a recurring sarcoma of the maxilla, Neander a neoplastic stenosis of the rectum, Aronsohn a cancer of the larynx, and Jenssen a cancroid of the tongue. But a study of these cases gives rise to some doubt regarding their nature. For example, Aronsohn's patient was a syphilitic with multiple laryngeal nodules, in whom the diagnostic reaction of Schmidt was negative. In Jenssen's case, again, the patient had an ulcer of the tongue in which the *Treponema pallidum* was easily demonstrable; cure resulted only after six months and a half of treatment, and was followed by abscess formation and subsequent scarring (gumma?).

Furthermore, Schmidt's conclusions have been severely criticized by Dreesmann on the basis of observations which he considered of positive value, and by Shaw-Mackenzie. Glenton Myler, also, in 9 cases seen in the Middlesex Hospital, noted the absence of any diagnostic reaction and of any therapeutic effect.

Beresnegowsky, in 7 cases of inoperable carcinoma at the Heidelberg Clinic, had nothing but negative results, while Winkler observed no effect on the tumors and called attention to the serious disturbances produced by the injections.

Beresnegowsky reported 2 patients who died without having been benefited and were examined histologically at biopsy and autopsy under Orth's direction. From these cases, one a recurrent gelatinous carcinoma of the breast, the other an infiltrating cancer of the larynx and epiglottis, Beresnegowsky concluded that neither from the clinical history, the autopsy, nor the mi-

croscopical examination, could any influence on the tumor be admitted, for the growth was not modified, metastases were not prevented, and the structure was not altered; the only definite result, he added, was the production in the first case of large multiple subcutaneous abscesses.

Czerny, wishing to reinforce the action of radium, tried out the combined action of serum and toxin. For this purpose the cancroin of Schmidt was tested on 45 patients, 14 of whom carried out the complete treatment, while others continued it only for a time or refused to go on with it because the first injection caused inflammation and fever. Czerny pointed out that in cachectic patients with visceral metastases in important organs the treatment should not be attempted, and concluded that although in some cases there might have been seen a temporary modification of the disease, cure was not brought about in any. Similar reports have been made lately by Werner, Sick, Kolb, Bagge, Nordt, and Stockmann; in no case of genuine neoplasia has antimeristem shown any elective action worthy of note.

Wlaeff, an adherent of the theory of the blastomycetic origin of tumors, prepared a specific serum and immunized animals against blastomycetes obtained by culture from human tumors; and having noted that the serum protected rats and monkeys from blastomycetic infection, he tried it in human beings. Serum obtained from pigeons, chickens, geese, or donkeys and administered subcutaneously every five to eight days in doses of from 7 to 12 cm. to patients without metastases, was said to produce an improvement in the general condition, a reduction in the volume of the tumor, and an arrest of its development. Permanent cure did not take place, however, the neoplasms later resuming their growth.

Biondi, in a discussion of the serotherapy of tumors presented before the Italian Surgical Society in 1895, stated that the serum of animals immunized with the blastomycete of Sanfelice was without any influence on either sarcomas or epitheliomas, while Lucas-Championniere, Le Dentu, and Berger obtained only transitory arrest with Wlaeff's serum.

The significance of blastomycetes as neoplastic agents has been denied also, and on the basis of accurate and extensive research, by Laederich and Duval, Franchetti, Stropeni, Cao, Tiberti, Donati, Alessandri and Zapelloni, Magnini, and finally by Galeotti, who was formerly inclined to ascribe etiological importance to them.

In regard to the therapeutic action of the serum prepared by Sanfelice and used by him in cases of lymphosarcoma and carcinoma of dogs, it must be objected that spontaneous regression of this type of lymphosarcoma has been reported by Sticker, Bashford, Beebe and Ewing, and Veratti, and that many observers are not willing to include the growth among the true tumors.

In three cases of cancer of the breast in dogs, which were treated with the serum, disappearance of the growth did not take place, but Sanfelice reported degenerative changes and a connective tissue reaction; this, however, Veratti and Vidal considered evidence of partial spontaneous regression.

Doyen has given the name *Micrococcus neoformans* to a parasite which he believes to be the cause of tumors. Intraperitoneal inoculation in white mice is said to have caused the formation of tumors about the liver and pancreas, and an inflammatory reaction of the lung with hyperplasia of the bronchial epithelium. And foci of melanosarcoma were said to have followed the intraperitoneal injection of an emulsion of a human pigmented tumor mixed with *Micrococcus neoformans*. In rats, inflammatory changes were observed in the large intestine, with changes in the glands, and Doyen described also a papillary carcinoma of the bladder, a cystic fibroma of the tube, epithelial growths of the lung accompanied by myxocartilaginous new growths, and several lipomas.

But the variety of type assumed by these growths, no less than the lack of precision with which they are described, suggests doubt as to the actual nature of the lesions encountered, and the suspicion is aroused that they were either chance findings or simple inflammatory reactions. The example considered by Doyen the most valuable only increases these doubts, for the

"melanotic sarcoma" above mentioned may be explained by mere phagocytic pigmentation of the reactive tissue at the site of the injection.

Doyen administered preparations of his bacillus for therapeutic purposes, also, but as the cases were treated at the same time by surgery, *x*-rays, radium, thermocoagulation, and heat otherwise applied, there was such an accumulation of therapeutic procedures that it is difficult to determine what part of the result can be attributed to the antineoplastic vaccination. The diagnoses were not confirmed microscopically, and even clinically were far from certain. Histological reports are generally absent, even in the cases that were subjected to operation, though they would have been of great interest in establishing the diagnosis and determining the changes referable to the treatment.

Furthermore, Hornus, in his inaugural dissertation on this subject, prepared under the guidance of Doyen, speaks only of delayed development, amelioration of the symptoms, improvement in the general conditions, and prolongation of life, producing no evidence that might lead one to accept the treatment as a cure. Nor did Berger, Monod, Nelaton, Kirmisson, and Delbet observe any improvement in 26 patients treated by Doyen, and followed for five months; unfavorable observations have been reported also by Vidal and Bender, Paine and Morgan, Pattison, Thomson, Musgrave, Woodman, van Ermengem, and Debaisieux.

Nobody, in short, has yet succeeded in obtaining reliable results from methods of treatment based upon a specific causative agent. These results, furthermore, have been no better than those obtained on the basis of a parasitic etiology acknowledged to be erroneous, as, for example, in the case of Adamkiewicz's hypothesis or of procedures based upon germs to which no pathogenic importance is attached, like the streptococcus of Fehleisen, or the *Bacillus prodigiosus* in the methods of Coley and Emmerich and Scholl.

PASSIVE IMMUNIZATION WITH TUMORS

Another group of investigators, without trying to determine the identity of the specific agent concerned in neoplasia, has attempted to secure active or passive immunization with tumor, on the hypothesis that some virus is contained in its tissues or that the tumor cells themselves are a virus.

This group includes Richet and Hericourt, who in 1895 immunized animals with osteosarcoma; the tumor was finely triturated and filtered through gauze and the liquid so obtained was injected intravenously into donkeys, dogs, or horses. The serum of these animals, collected seven to twelve days later, was introduced subcutaneously in doses of 3 cc., either in the neighborhood of the tumor or at a distance from it. It was asserted that noteworthy improvement in the general condition set in, that the tumors diminished in size, hemorrhages were arrested, ulcerated surfaces became clean, and that partial cicatrization resulted, though without permanent benefit being obtained. After a very short period the tumors again began to grow and the general unfavorable condition progressed in spite of continuation of the treatment. This was further accompanied, moreover, by evidences of intolerance, among which vomiting, diarrhea, lumbar pain, skin erruptions, headache, and fever were notable. Similar findings have been reported by Boureau, Boinet, Brunner, Bosc, Ceci, Barlerin, Biondi, Pascale, De Gaetano, Salvati, and Parascandolo.

Various modifications of the serum treatment have been suggested, especially since the early researches of Metalnikoff, Ehrlich, and von Dungern on cytotoxins. These suggested a specificity of cytolysins, and gave rise to the hope that a cytolysin might be prepared which would attack only tumor cells. The attempts begun by Richet and Hericourt were therefore continued by other investigators, among whom were Poncet and Dor, Charcot, Jensen, von Leyden and Blumenthal, Hoyten, Borrel, Lomer, Loeffler, Vidal, etc.

Dor, in 1900, injected a goat with a melanotic tumor and introduced the serum so obtained into two persons suffering

from melanosarcoma. After a period of subjective and objective improvement the first patient was lost sight of, while in the second case the treatment was interrupted by lack of serum.

Leyden and Blumenthal treated goats and sheep with epithelium from the breast, liver, or uterus, and injected the serum into persons suffering from epithelial new growths of the corresponding organs, but except for temporary improvement and transitory changes in the consistency and volume of the primary tumor and its metastases, no action was discernible.

Hoyten injected fluids from human carcinoma into dogs and inoculated their serum into patients; the results were more evident in the metastases than in the original tumor.

Lomer reported a case of recurrence in the scar of an operation for carcinoma of the breast. Half of this nodule was used for histological diagnosis, and the remainder disappeared following a series of injections of animal serum obtained after treatment with human epithelium. In the same way an axillary metastasis that appeared later was caused to retrogress.

Vidal has recently affirmed that it is possible to obtain a serum of considerable efficacy by injecting animals with human tumor of the same type as that which is to be treated. For this purpose he carried out the method of Besredka for antibacterial serums, injecting a fresh emulsion of tumor cells sensitized with the corresponding serum previously obtained. Furthermore, during the treatment of the animal from which the serum was to be obtained, he injected substances capable of bringing about a hyperleucocytosis in order to increase the antibody content. Curative sera thus prepared, which should possess specific properties and particularly that of cytolysis for the tumor cells, require a long period of administration because their action is slow. During this time, according to Vidal, the body of the patient reacts by the production of neutralizing substances forming an immune antiserum. To avoid this drawback, he prepared another serum from dogs treated with neutralizing blood from patients who for some time had been subjected to the immune serum, or with pleural or peritoneal effusion fluid from the same patients; in this way he obtained an anti-immune serum, or

serum N. After prolonged injections of an immune serum and of this serum N, Vidal obtained in some patients complete regression of their tumors.

But in spite of the various modifications suggested by Richet and Hericourt, serotherapy has not fulfilled expectations, and has even lost a great part of its experimental basis. Thus Jensen, who was among the first to carry out attempts at specific serotherapy in animals, has acknowledged that the regression observed by him in the transplanted tumors of mice that had been injected with serum from immunized rabbits, was spontaneous; that is, it often occurs without the use of any specific serum. This agrees with the experience of Bashford, Murray, and Cramer, who did not observe any effect from serotherapy when treated mice were compared with untreated controls.

Loeffler, who attempted to obtain an active serum from immunized donkeys, was obliged to admit that such a serum precipitated normal elements in the same degree as tumor cells.

In addition to a lack of specificity in the serum of immunized animals, and to its inefficacy, it is to be noted that the partial and temporary results referred to immune sera have also been described after the use of normal serum (Arloing and Courmont, and Augagneur).

ACTIVE IMMUNIZATION WITH TUMORS

Beside passive immunization, active immunization by vaccination with tumor has been attempted, in the hope of obtaining specific antibodies in the patient himself. Thus, Hoyten, in 1899, injected into the neoplasm tumor juices diluted with physiological salt solution, and reported favorable results.

von Leyden and Blumenthal spoke favorably of active immunization carried out according to their hypothesis. In the first notes published, it was stated that the expressed juices of new growths obtained from human beings at operation were tried on three patients. The tumors themselves did not undergo any important change, but indurated lymph-nodes in the neighborhood grew smaller and improvement was noted in the pain and

in the general condition; the nature of the lymphadenoid enlargement, however, was somewhat doubtful, since the neoplasms were ulcerated and therefore infected. Two of the cases are reported to have died.

Müller, trusting in the bactericidal action of glycerin, prepared his material by placing fresh tumor in 80 per cent glycerin; the mixture was kept for forty-eight hours at 37° and then diluted with physiological salt solution and injected in the mammary region. Seven cases were treated, six of which had carcinoma of the uterus and one an ovarian cyst undergoing carcinomatous change. The injections frequently produced abscesses and febrile symptoms, but no cure.

Other attempts at active immunization with tumor have been made without decisive results by Caan, Rovsing, Odier, Delbet, Graff, and Ranzi. Delbet, for example, injected into patients after radical operation the entire tumor reduced to a pulp; this material, without the addition of any bactericidal substance, was suspended in a small amount of physiological salt solution and introduced subcutaneously in two, three, or four different regions, according to its volume. It must be mentioned, however, that he preceded the operation and injection by a course of radiotherapy and the copious painting of raw surfaces with tincture of iodine, and followed it by the application of at least 3 cgm. of radium bromide between the sutured surfaces. This was allowed to remain in position for twenty-four hours, and ten days later *x*-ray treatment was again instituted. Only a short time was necessary to show that the method produced implanted tumors, a consequence which supervened in the cases of von Graff and Ranzi also.

Coca and Gilman have also taken up the matter of active immunization, inspired by the researches of Metalnikoff, von Dungern, and Hirschfeld. The patient's tumor was reduced to small fragments with scissors immediately after removal, repeatedly subjected to pressure, suspended in physiological salt solution, centrifuged, decanted, and finally treated with 0.5 per cent of phenol or toluol. The injections were generally carried out about six hours after the addition of the phenol, though

sometimes earlier when the extract was uncontaminated. The dose of the tissue for each treatment varied from 10 to 25 grams, the fluid being introduced into the abdominal wall through four to six different punctures. The inoculation often gave rise to a local reaction, but in no case did sufficient time elapse to enable one to come to a decision regarding the value of the method; in most cases there was a period of only a few days or months between the operation and the report. Furthermore, microscopical examinations and clinical reports are lacking.

The dangers inherent in active immunization when it is carried out by methods above mentioned have been clearly indicated by Wolff and Blumenthal. Wolff makes the following comment: "Autovaccination, as we have so far come to know it, always involves the danger that living cancer cells (or if one upholds the parasitic theory as von Leyden and others do, living parasites) may be introduced, to give rise later to the formation of new tumors."

HISTOGENETIC CHEMOTHERAPY

While stress had been laid on the principles of active immunization as recently as 1910 with the technic and the results just recounted, I had undertaken comparative observations on embryonal and tumor implantation as well as on the action of histogenic autolysates some years previously, and had treated tumors in animals and in man with fetal tissue or with tumor cells. My research and that of my collaborators was founded on the hypothesis of oncogenic disequilibrium, which would refer the origin of tumors to a state of disharmony, a disturbance of the factors regulating proliferation, during which they pass from under the control of the enzymes, hormones, and histolytic products which ordinarily guide them.

Histotherapy on a biochemical basis, or *histogenetic chemotherapy*, attempts to cure oncogenic disturbances and their effects by stimulating oncolysis. It is naturally limited by its own nature, as it is not possible to suppress all the abnormal functional activities to which the origin of tumors is due, nor is it possible to exceed the limited dose that can be injected.

The earliest experiments were carried out with autolysates and filtrates; the clinical course of transplanted tumors in relation to the host, spontaneous involution, and acquired resistance were also investigated, and the conclusion was finally reached that resistance depends on the absorption of histogenic substances and on the reaction produced by these. Later I undertook an investigation of the regression provoked by histogenic substances, either embryonal or neoplastic, and was able to establish a parallel between autolysis in vivo, by immunization, and autolysis in vitro by the method of histogenic therapeutics. The treatment was applied also to 36 patients with inoperable malignant growths, with a result which was summed up in 1910 as follows:

Objectively there may be an arrest or even a disappearance of the tumor, and anatomical changes may be observed which are sometimes definite enough to permit the assumption of local cure at least. Thus in favorable cases there may be observed a cytolysis of the tumor cells, gradually increasing until these have entirely disappeared; an intense small cell infiltration which is more pronounced about the blood-vessels; the appearance of numerous microphages, macrophages, and plasma cells; active connective tissue and vascular infiltration invading all portions, together with some giant cells; replacement by dense connective tissue; in short, the cessation of all phenomena associated with infiltration and growth. The tumor becomes soft and fluctuating, and aspiration in these cases reveals a clear fluid containing whitish flakes in suspension and having the character of a transudate. All these changes are perfectly comparable to those which I have already described in rat sarcomas treated by means of autolysates, and may be compared, also, to those characteristic of sarcomas or carcinomas which have been transplanted into rats immunized with embryonal tissues. They are similar, too, to those seen in receding tumors and in grafts of embryonal tissue in the second period of their cycle; that is, in the phase of regression and disappearance. It is a question, therefore, of physiopathological phenomena which can be explained according to general laws and which go on with greater intensity in accordance with the combined action of various factors.

The value of histogenic chemotherapy was promptly confirmed by numerous other investigators, and autolysates or

extracts have since then been generally used; by some authors in the way just described, by others through vaccination, which, under these conditions, does not involve the risk of implanted tumors which is present when emulsions are used.

For example, Abderhalden and Kohlhardt have referred explicitly to these researches in their experimental and clinical observations. They attempted to utilize only the antiblastic reaction obtained according to the technic and principles of protective ferments, which they were among the first to study intensively and which have been accepted by many others, at least so far as the specificity of tissues and lytic ferments is concerned.

Blumenthal desired to see the discussion limited to neoplastic tissue, since he denies that the same therapeutic or immunizing results can be obtained with normal tissue as with homologous tumor. But to deny the presence of resistance after treatment with normal tissue is to do away with the researches of Bashford, Schöne, Michaelis, Borrel and Bridé, Lewin, Apolant, Moreschi, Da Fano, Levin, Brancati, Magnini, Biach and Weltmann, Higuchi, Woglom, Loeb and Fleisher, Krongold, Jowleff, and Roffo; yet these have definitely proved the existence of immunity following treatment with skin, embryo emulsion, blood, mammary gland, liver, spleen, and thyroid. To deny this refractory state is, in fact, to deny some of the most important findings in the entire field of cancer research, and, leaving aside the various ideas concerning specificity, would mean abolishing the basis on which vaccination is founded, firmly established as this is by the tuberculin reaction and the resistance to transplanted tumors caused by absorption of injected tissues.

Recent observations, carried out especially in Italy, suggest an easy explanation of the curative mechanism of tissues in general. These have included the investigation of cancerous organs; of inoculation of tumor grafts into various organs; of the immunizing and therapeutic power of extracts from normal and pathological organs; of the effect upon receptivity or resistance of the removal of different organs; of differences between

normal and immune animals; and of the oncolytic variations in the serum of normal or tumor-bearing animals. Among the Italian investigators who have worked on these subjects are the following; Fichera, Ricci, Perez, Gussio, Almagia, Brancati, Magnini, Cimoroni, Caravani, Mazza, Piantoni, Donati D'Agata, Serafini; the list of those in other countries includes von Graff, Apolant, Korentschwesky, Sweet, Saxon, Hilario, Loeb, and Freund and Kaminer.

The results of their observations lead to the conclusion that certain organs possessing active oncolytic and hyperplastic properties in normal or immune animals, are inactive in advanced life or in the presence of a large tumor; and furthermore, that the histogenic substances which have been found efficacious act both directly and indirectly.

The *direct* method depends on cytolytic ferments contained in the various tissues and organs (the isoferments of neoplastic autolyzed tissues, and the heteroferments of normal tissues or those undergoing active histolysis). The *indirect* is represented by stimulation of the organs producing oncolytic substances; under favorable conditions this can be effected by the constituents of various tissues.

These observations and conceptions are important, enabling one to understand, for example, the varying efficacy of the different tissues in proportion to their original content of oncolytic substances and the different degrees of antiblastic reaction which they can produce.

The observation by Bertrand, Daels and Deleuze, Sellei, Lunckenbein, and Schubert, that unsuitable dosage may cause an increase in the growth of a tumor instead of regression, was demonstrated some time since by me; and Gussio, Brancati, and Caravani hold similar views. This unfavorable action of large doses explains the negative results obtained in man by Austoni and Carraro, while, in considering the work of Uffreduzzi and Morpurgo on rats and mice, one must remember that chloroform rapidly inhibits the therapeutic action of autolysates, as has been shown by Levin, Lewin, Bauer, Latzel, and Wesselly. Again, degenerative changes may be followed by

extension of the growth, with liberation of autolytic products and the institution of a negative phase marked by increasing failure of the oncolytic system and a hastening of the clinical course. The same condition follows intense radiation or the administration of large amounts of colloidal substances; these, instead of stimulating, seriously injure the inhibitory organs and bring about those unfavorable effects described by some writers. There is a connection between the methods just spoken of and the stimulation of chemotherapy. Indeed the direct action of the best known physical and chemical agents is accompanied by a no less important indirect effect recently illustrated by my experimental results, as well as by those of Brancati, Gussio, Caravani, and others, among whom Fränkel and Kimball should be mentioned especially; these have demonstrated an increased resistance in healthy animals suitably radiated before inoculation.

Indirect action deserves the more interest in that there is less definitely a specific factor concerned, the condition reducing itself to a greater sensibility of the neoplastic elements. Their susceptibility subjects them to the general laws of Guilleminot, according to which cells are the more sensitive to radiation the greater their karyokinetic activity, and, therefore, the shorter their vital cycle.

On the other hand, it is noteworthy that doses of radioactive substances only a little greater than those employed, and usually insufficient to cause the disappearance of tumors, are frequently responsible for serious lesions of the body tissues, which, according to the intensity and frequency of the radiation, may pass from hyperplasia to necrosis (Fränkel and Budde, Miller, Heinecke, Unseitig, and Steinhaus).

Thus, radioactive substances exert no specific action on the tumor cell, an impression that has been once again confirmed by Pentimalli. The truth of this statement is evident from the limited destruction of tumor and the extensive damage to healthy tissues produced by strong and penetrating doses. The satisfactory results hoped for through the employment of large amounts have not, therefore, been gained, as not only clinical

observation, but the histological investigations of Aschoff, Steinhaus, Versè, Simon, and Dürck only too clearly demonstrate.

The same may be said of the various chemical substances that have been suggested. For example, the metals which have been reported on by von Wassermann in animals and by Quarelli in man, do not show any specific deposition in the tumor, when normal and pathological tissues from the same organ are compared by extraction, or by polarimeteric and histochemical methods. The result is rather that the liver and spleen are generally found to be richest in the substances used. When the quantities introduced are excessive, there are found intense hyperemia, hemorrhage, and degeneration in many organs; especially is this true of the hematopoietic system, as a consequence of which there occur changes in the blood picture (Robin, Ashard, Bardet, Girard, Dugern, de Ario).

On the whole, then, it may be said that the tumor cell has so far offered no specific point for attack by radioactive substances or by chemical agents. Yet in the organs of animals exposed to these measures, structural and functional conditions are encountered which throw some light upon the indirect action of the agents in question.

Thus when too active radiation is employed, or too large amounts of metals, autolysates, or extracts, there are found degenerative lesions and hemorrhages into the parenchyma of the more important organs, and into the tumor itself; and the neoplasm may even be stimulated to increased growth. But when the same measures are applied in suitable doses, a functional hyperplasia supervenes in the various organs, and especially in those appertaining to the hematopoietic system (Fichera, Brancati, Gussio, Caravani, and Szecsi), which is accompanied by arrested development in the tumor or even by its complete disappearance.

Again, in both animals and man, the *x*-rays or radium in suitable amounts may bring about leucopenia quickly alternating with leucocytosis. In this way one may cause succeeding cycles of leucolysis and abundant regeneration, as has been especially shown by Aubertin, Beaujard, Guilleminot, Manouk-

hine, Murphy, Morton, and Nurenberg. Similar results have been obtained by the injection of colloidal substances which have been found capable of producing effects on the blood-forming organs by von Hansemann, de Laire, de Ario, Szecsi, and Pentimalli. That the same thing happens after the use of histogenic autolysates is shown by the general condition and by the state of the blood, according to my observations and those of Almagia, Vaughan, and H. Ross.

Under these conditions one may find an augmentation in the size of the liver and spleen, as well as an increase in the function of the blood-forming organs; the latter involves not only the bone-marrow and spleen, but also the liver, even in animals that are no longer very young. These changes, on the other hand, belong especially to the first years of life, that is, to a period in which spontaneous tumors are seldom seen, and are also observed in immune rats, so that they may be considered as an anatomical substratum of resistance (Fichera, Brancati, Goldmann, and Mazza).

The fact, therefore, that these visceral changes are found both in tumor-bearing animals and in normal ones treated by the various agents mentioned above, suggests the possibility of a participation of these functional activities in the regression of tumors.

If organs inhibiting neoplastic development can be rendered more active by suitable treatment, it is not possible to deny that oncolysis may be brought about, indirectly, by their hyperfunction.

In explanation of the lack of response shown by recurrent tumors to the various means of treatment, a possible acquired resistance of their cells has been proposed. But another reason for the difference in behavior between man and animals, or between spontaneous and implanted tumors, suggests itself. The animals used for experimental purposes are young and healthy, and their oncolytic defense is accordingly perfect. They therefore react to stimulation and defend themselves well, whereas in a human being, because of the physiological involution inseparable from age which characterizes the on-

cogenic period of his life, the organs are atrophic, so that the body is less able to respond to stimulation. The increase of this biological disadvantage with time, and with the exhausting demands of treatment, explains the unsatisfactory therapy of recurrences after a previous attempt to cure.

SUMMARY

Certain fundamental principles of treatment may be derived from what has been said:

Importance must be attributed to suitable dosage, to the proportion between the mass to be destroyed and the curative agent, and to the alternation of oncolytic stimulation with various histogenic products. Finally histogenic treatment adds to its indirect action on antiblastic organs an important direct action by reason of the oncolytic substances introduced.

In developing the biological treatment of tumors, chemotherapy should be especially practised by means of autolysates, the importance of which has been emphasized by such authors as Vaughan, C. Lewin, Daels and Deleuze, Theilhaber, Lunckenbein, Koenigsfeld, Rohdenburg, Bullock, and Johnson, Briggs, Bristol, Bulkley, Little, Stammler, Mioni, Citelli, Bauer, Latzel, Wesselly, and Klinger.

For the bibliography the writers quoted in my principal publications should be consulted; from these the present abstract has been made.

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OCCUPATIONAL CANCER*

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PART 1

The expression "occupational cancer" in reality refers only to a predisposition to the disease, caused by the action of a group of commodities used in certain trades and occupations. The substances in question do not directly cause cancer, but affect the tissues in such a way (usually by giving rise to cell-proliferation of an adventitious type) that the site is rendered specifically prone to malignant invasion. It is well known that soot is one of these commodities, and there is considerable evidence that tobacco-smoke helps in causing the incidence of epithelioma in the throat and larynx. It has generally been considered that this predisposition is due merely to mechanical "irritation" of the tissues, and therefore the subject has not hitherto received much if any systematic investigation, for it is common knowledge that chronic mechanical injury in certain tissues during senescence is liable to predispose to malignant invasion; but during the recent government enquiry into pitch cancer at the briquette works in South Wales some new clinical facts have been found out, which make it appear that some definite, if not specific, chemical rather than mechanical action is concerned in the causation of industrial cancer.[2] This has led to the investigation of other commodities the use of which also gives rise to cancer under certain conditions; and when all of them are examined collectively, there seems to be considerable

* The author has not read the proof of this article.

[1] Late Director of the John Howard McFadden Research Fund.

[2] The writer was called upon to give evidence at this enquiry, and it was in connection with it that the following investigations and experiments were made.

evidence, both circumstantial and experimental, to show an association between certain chemical products of death and putrefaction contained in or produced by the commodities themselves and the onset of the disease.

As this evidence is clearly of value in the investigation of the general etiology of cancer, the several commodities will first be discussed *seriatim*, describing the sources and general properties of each substance, the clinical manner in which the disease is brought about, and their power of causing chemical versus mechanical "irritation." Later on the property of producing "smarting of the skin," a chronic dermatitis which is possibly in some instances the initial lesion, and which is an important industrial complaint in some of the trades, will be described. In the description of the commodities references will be given to the description of other commodities, so that comparisons can be made on the one hand as to the incidence of cancer and on the other as to the amount of mechanical injury caused.

It is convenient to take first the coal-tar derivatives and in the order in which they are produced commercially; but this order is inverse to the amount of disease to which the said commodities give rise.

COAL

Coal may be described as a residue of prolonged compression of vegetable matter which has undergone death and decomposition. Coal-miners, heavers, stokers, etc., become covered with coal-dust during their occupations, and yet, in remarkable contrast to its more concentrated products such as tar, pitch, and soot, coal does not give rise to warts and epithelioma. Occasionally a case is reported from one of the mines, but the incidence is rare. In the navy the writer never saw a case among the stokers, and the disease is not specially remarked upon by authorities on miners' diseases.

Mechanical injury. Coal-dust is hard and gritty, and, if it is rubbed on the skin, the fragments are so sharp that they may cause mechanical injury almost amounting to laceration of the epidermis. But coal-dust can be readily washed off the skin.

At the gasworks coal is distilled for the production of gas; at the blast-furnaces it is used as fuel. Bituminous coal is mostly used in England at the gasworks and coke-ovens; for reasons which need not be mentioned here, the harder Scotch coal is mostly used at the blast-furnaces. In both these industries tar is produced as a by-product, and the varieties are generally known as gas-tar and blast-furnace-tar respectively.

TAR

Tar may be described as concentrated coal.[3] It is the residue after the first stage in the distillation of coal. By far the greater quantity of it is produced at the gasworks and coke-ovens. Gas-tar varies considerably in its reaction and viscosity according to the temperature of its distillation and to the type of coal from which it is made. Chemically, it contains a large number of substances, some of which will be described later. Blast-furnace tar is very similar except that it is made from a different coal and that it comes over at a lower temperature.

Gas-tar causes warts and epithelioma on the hands and arms of the workmen who handle it, although the incidence is not so great as that caused by pitch or soot (see later). The action of tar is similar to that of crude paraffin, which will also be detailed later. Butlin quoted this action, as described by both Volkmann and Ogston, thus:

> Substantially, the effects of the liquid tar and paraffin on the skin of those engaged in the manufacture and whose bodies are actually exposed to them, consisted in eruptions of an acute and chronic character. The acute forms sometimes passed off, and were so completely recovered from, that they scarcely left any trace behind them, but they passed on in many of the people to become chronic. In the acute form the hair follicles and sebaceous glands were chiefly affected, often with the production of an eruption of bright red nodules closely approx-

[3] The word "concentrated" is a convenient one to use in this connection as will be seen later, but it should be remembered that, in each stage of the carbonisation of coal and its derivatives, certain fractions are removed; but as the disease caused by each stage is more pronounced, the fractions removed evidently do not concern us.

imate to each other, and usually largest and most numerous on the wrist . . . . the dorsal aspects of the parts being most severely affected and the palms of the hands and soles of the feet enjoying a complete immunity. The red nodules correspond with the hair follicles. With the diminution and disappearance of the red eruption, the hair follicle remained enlarged, its mouth gaping and occupied by a little mass of epithelium and dirt, so that the black points were visible over the surface of the affected skin. The only difference in the descriptions of Ogston and Volkmann is that the former speaks of the hair follicles, the latter of the sebaceous glands, as the structures affected and the seat of the black points. In the chronic condition the skin between the hair follicles or sebaceous glands was also altered, it became thickened, dry and stiff, chiefly by increase in the thickness and alterations in the quality of the epidermis. Volkmann describes, in addition (probably because his observations extended over a longer period and were made on a larger number of individuals), little knots of epidermis, tiny horns, and flat, dirty brown scales and crusts. He found that the infiltrations on the skin were most frequent on the forearms and scrotum, where particularly they were prone to become moist and offensive.

It is the chronic condition that is liable to become malignant. Unfortunately there is no accurate return of the number of cases at the tar works, for these industries have not yet been scheduled as "dangerous trades," but from enquiries from the tar-distillers, cases of malignant invasion of the warty skin are not uncommon.

Blast-furnace tar, on the other hand, seems to be harmless.

Mechanical injury. There is an absence of fine particles or grit from tar, which is a viscous liquid at ordinary temperatures. In the strict sense of the term, therefore, it can hardly be accused of causing *mechanical* irritation, but when it dries on the skin, especially after vigorous washing, a little mechanical injury may be caused before it can be entirely removed from the pores.

Both gas-tar and the blast-furnace variety are consigned to the tar-distillers, who, by further carbonisation, obtain various commodities from it, such as ammoniacal liquor (sulphate of ammonia for manure), naphthas, creosotes, phenols, anthracene oils, and many others.

The residue is the black bitumen, which sets on cooling, known as gas-tar pitch and blast-furnace pitch respectively. Four-fifths of the pitch made is consigned to the briquette works.

PITCH

Pitch may be described as concentrated tar. Gas-tar pitch causes the disease known as pitch warts, which is fairly frequently followed by pitch cancer. The common site, as in the case of soot, is in the scrotum, but the warts also appear frequently on the face, neck, and lip; next to the scrotum, the lip is the commonest site for malignant invasion of the pitch wart. From time to time opinions are advanced that pitch cancer is not true cancer; but they can be disposed of by the fact that the disease is identical with chimney-sweeps' cancer, and has within the last year to the writer's knowledge caused at least two deaths in Swansea alone.[4] It is true that the warts are not malignant at first, and there is evidence to show that they do not become malignant, in a manner similar to the case of tar, until ulceration has occurred, leaving an open sore at the base; but once they become malignant and remain untreated, the disease runs its usual course with metastasis and death, although, as the lesions involve the skin, the mortality is not very high owing to early detection and the facility for complete removal.

At the briquette works, pitch is ground into a fine powder and mixed with small coals, the mixture being damped by steam and compressed into the blocks which constitute the "patent fuel." The pitch grinders suffer most, although there are some cases among the men who handle the briquettes. Out of 246 men examined by Dr. Legge, H. M. Inspector of Factories, 51 suffered from pitch warts and 28 showed signs of old ones. It is probable, as Mr. Commissioner Lush (1) has pointed out, that the incidence is higher than this, as the numbers examined included men other than the pitch grinders. In the writer's experience at the works, the incidence of pitch warts among the grinders is practically universal except in the cases of boys or young men.

[4] 1914, since then the disease has frequently occurred.

It is remarkable how pitch warts become more common in the men as age advances, a point brought to light at one of the Home Office conferences with the briquette trade, and apparently in harmony with the etiology of tumors in general. The actual clinical condition cannot be better described than by the following quotation from Dr. Legge's Report (2), in which it is pointed out that the men engaged in the manufacture of briquettes

> are liable to suffer from warty growths, which ulcerate and occasionally become the seat of epitheliomatous cancer. The growths may occur on any part of the body, and are common on the face, hands, and scrotum. [The region where the collar rubs is a very common site.—H. C. R.] They commence as small nodules in the skin and almost immediately begin to break down, forming an ulcer covered by a crust, which gives the characteristic appearance to the so-called wart. The underlying ulcer almost invariably heals up, leaving a small scar when the crust has fallen off. We believe this to be the normal course, although witnesses regard the scar as the result of the primitive methods of treatment adopted by the workers. When they take on an epitheliomatous character the situation is almost invariably on the scrotum. The disease then follows the usual course, involving neighboring organs and tissues and can only be arrested by free excision. Epithelioma is the least malignant form of cancer, and on removal is not usually followed by recurrence. We saw men still at their ordinary work and in good health, on whom such operations had been performed several years previously. The amount of incapacity caused by the condition, whether in its benign or malignant manifestation, need not be great. There was general concensus of opinion that the cancerous conditions could be prevented by scrupulous cleanliness, but we satisfied ourselves that *occasionally* it may develop in those who have paid all reasonable attention in this respect.[5]

Blast-furnace pitch does not appear to cause either warts or cancer (1), (2). The difference is a most important one; and the government, in imposing regulations (1) to deal with pitch cancer, specifically exempted those factories in which only blast-furnace pitch is used. Yet the two forms of pitch are

[5] The italics are mine—H. C. R.

practically identical except that the blast-furnace variety is made from tar which comes over at a lower temperature, and which is mostly made from the less bituminous Scottish coal.

Mechanical injury. Both forms of pitch are gritty, but less so than coal and more so than soot. At the hot temperatures of the briquette factories, ordinary pitch softens slightly on the men's skins, when it is sometimes difficult to remove; blast-furnace pitch, however, does not so easily soften.

SOOT

This substance, which may be described as concentrated pitch, is the best known cause of industrial cancer. The mortality from it among chimney sweeps is twice what it is among occupied males generally. The mortality in 1900–1902 was 133 as compared with 63 among occupied males at the same age. "This excessive prevalence is certainly due to the nature of the trade, the soot setting up an irritation of the skin similar to that produced by pitch or tar and with similar results." (1)

The form of soot that gives rise to this disease is that produced by the carbonisation of coal; and more soot is set free by burning bituminous coal than by the use of the harder varieties, such as anthracite. Soot,[6] however, is not pure carbon but also contains tar and tar oils with a certain amount of varying degrees of pitch. It is not gritty as a rule, but of a soft floury nature due to the tar oils, as can be readily demonstrated by placing some on blotting paper, when the oils will produce a greasy exudation. Owing to this oily nature, soot can only with difficulty be removed from the pores of the skin; but although the sweeps' bodies are covered with it from head to foot, like pitch, it causes the disease practically on the scrotum only—preceded, as usual, by warts. This is a remarkable fact, but at the same time it should be remembered that with this class of workmen,

[6] "There is 'sut' and 'sut,'" an expression frequently heard at tar and briquette works. Soot is the cause of chimney sweeps' cancer and is collected from domestic chimneys. "Sut" is practically clinker, consisting of carbon and earthy salts, like the smoke-box ashes produced in locomotive flues. High temperature and pressure furnaces produce the latter, which is harmless.

who rarely have baths, the scrotum is the dirtiest part of the body, and is constantly subjected to rubbing from dirty corduroy trousers. Moreover it is a part where sweating is profuse.

Mechanical injury. The absence of grit is an important point, because the floury soot differs in this respect very materially from coal-dust, which does not cause cancer at all, yet which will cause mechanical injury amounting to laceration.

We may now sum up the foregoing commodities to show the relative amount of mechanical irritation caused by each, comparing that with the amount of cancer caused by each.

MECHANICAL INJURY	COMMODITY	CANCER INCIDENCE
Greatest	Coal-dust	Nil
Considerable	Blast-furnace pitch	Nil
Only little, as it softens	Gas-tar pitch	Considerable
Practically nil, a liquid	Tar	Several cases, but less than pitch
Nil	Soot	Greatest incidence of all

It seems clear from this clinical evidence that pitch warts and epithelioma in the coal-tar industries are not due merely to mechanical irritation, for the more the irritation the less the disease.

Since the predisposition is not due to mechanical injury, it is obvious that it must be due to chemical injury, which is borne out by the fact that it is the most concentrated form of coal, namely soot, which causes the most disease, the incidence among the intermediate trades rising in exact ratio with the concentration; thus, coal causes no warts or cancer, tar causes some cases, pitch causes many more, and soot causes a double mortality. The gradual concentration of the coal, therefore, also apparently concentrates at each stage of the distillation some substance which seems to be the predisposing cause of cancer in all these industries.

That some chemical factor is concerned is also evinced by the harmlessness of blast-furnace tar and pitch. These substances cause more mechanical injury than their gasworks prototypes,

and yet they have no cancer-producing action whatever. But the blast-furnace tar is produced at a lower temperature and from different coal, which makes it all the more probable that the mischievous chemical substance is less effective or absent from this commodity.

ANTHRACENE FRACTION OF TAR

There is a theory at the works that the mischievous substance is contained in the anthracene fraction of tar, because of recent years it has not paid, as formerly, to remove this fraction for the manufacture of dyes, and the leaving of it in the pitch coincides with the increase of the disease in the last decade or two.

NAPHTHALENE

It is also clear that the products of the lighter fractions are not to blame, because those who make boot-blacking and other "blacks" do not suffer. Boot-blacking is made by the carbonisation of naphthalene (isolated from a tar fraction lighter than the anthracene fraction) which is converted into a "soot" by burning on hot plates. The workmen in this industry become covered with this "soot," but Dr. Legge states that there are no cases of pitch warts or cancer among them. This is another piece of evidence against mechanical injury, for naphthalene soot and coal soot are similar as regards the physical nature of the particles, yet one is harmless and the other most dangerous.

OTHER TARRY COMMODITIES

Liquor carbonis detergens, creolin, etc., are used extensively on the skin. In some cases they cause thickening. They seem to promote the cell-proliferation of healing, and are used under prescription for this purpose. They contain the middle fractions of tar, which seem to be responsible for the proliferation which leads to the warts in the industries.

In this respect it may be useful to draw attention to the tar capsules which from time to time are advertised to be taken

internally as an aid to digestion. Those that have been tested in these laboratories also contain, as a rule, the middle tar fractions, and therefore it would appear advisable for them to be prescribed only with great caution. The intestinal epithelium is much more liable to malignancy than that of the skin, and subjecting it to a specific commodity is to be avoided.

There is no evidence that dust from the tarred roads causes warts, but there have been some complaints of conjunctival inflammation from it.

"SMARTING" OF THE FACIAL SKIN DUE TO PITCH DUST

This point may be conveniently discussed before we leave the tar products, although it is doubtful whether it is connected with the pathological changes which lead to pitch warts. As Mr. Lush points out (1), all fuel workers suffer from a burning sensation in the face especially when exposed to keen winds or sunshine, and one of the chief objections to the bathing regulations was that washing made this condition worse. The physical signs are not very noticeable; sometimes there is slight dermatitis with a little peeling, but never any discharge. There is never a "flare up" like that seen in eczema. The burning sensation is undoubtedly troublesome, coming on sometimes after an hour's exposure to the pitch dust—as the writer can personally testify—and it may last for several hours. The condition seems only to affect the cheeks and the region behind the ears, and it may be so bad as to prevent the men attending football matches.[7]

Some cargoes of pitch cause it more than others, and the bad varieties seem frequently to stain the skin a yellow color.

Experiments were made at the works to find out the cause of this burning of the skin. Some pitch was finely ground and then thoroughly washed with water and dilute acid; the water was allowed to dry on the skin, but no burning sensation could be felt. Two of the pitch grinders then rubbed the washed pitch

[7] More recently this or a similar burning of the skin has occurred to a considerable degree among munition workers who handle certain coal-tar explosives. An acute dermatitis is produced, with a yellowish discoloration of the skin. The question is being investigated.

powder on their skins, when it was found that it still caused the dermatitis. It is apparent, therefore, that this burning is at least due in part to slight mechanical injury. A watery extract from some of the pitch which was more irritating than that from other cargoes, and which contained the yellow ingredient, did, however, cause a little smarting when applied to the dorsum of the hand, and it is possible that this is due to an excess of acridine.

But the common sites of the smarting are not those of the pitch warts; the lips, eyelids, and scrotum are not affected. It is possible that the slight mechanical injury may leave fissures in the skin in which the pitch dust may become impacted, and so lead to pitch warts, and the swarthy skin, which is due to "blackheads;" but the part played by it, for the reasons given above, is probably a minor one.

Attempts to protect the men's faces by fullers' earth was partly successful, but the men refuse to use it; protection by liquid paraffin caused such acute erythema that it had to be abandoned.

There is little evidence that smarting of the skin occurs among coal miners; soot appears to cause it only to a small extent. Dr. D. A. Crow has kindly interrogated 36 sweeps on this point, and has elicited the fact that 26 of them complained of slight burning, one saying that boiler soot from coke was particularly noxious. It may be due to the sticky nature of softened pitch and soot, which may necessitate tearing of the epithelium when washing it off.

PITCH FROM PITCH LAKE, AND FROM MANJACK MINES, TRINIDAD, WEST INDIES

Dr. H. L. Clare, the Surgeon General, Trinidad, has been good enough to supply the following information.

> The Mines (Manjack) near Princes Town have not been worked since the beginning of the war. I have never heard of any unusual—or indeed of any incidence of cancer amongst the laborers; these mines are worked at a considerable distance below the surface, while the Pitch Lake work is all on the surface.

Dr. George Campbell, Resident Medical Officer of the Pitch Lake Company, reports to Dr. Clare, thus:

I have had no case of cancer among the pitch workers here during the last five years, and can find no history of such a case having occurred. I may say that the workers come very slightly into contact with the pitch, the actual process being largely one of cutting and loading. The pitch of the lake does not come from bituminous coal, but is closely related to the non-volatile constituents of crude oil, with no paraffin base. Composition: water and gas 29 per cent, bitumen 39 per cent, organic matter 7 per cent, mineral matter 25 per cent. Composition of the bitumen: carbon 82.33, hydrogen 10.69, sulphur 6.16, nitrogen 0.81.

The small content of nitrogen is most interesting, as will be seen later. The fact that the pitch is not bituminous is also worthy of note.

ANILINE DYES

There are practically no manufactories of aniline dyes of a large size in England, and it was difficult to obtain reliable information about industrial disease on the Continent, even before the war.[8] The Chief Inspector of Factories, however, refers to a series of 14 cases of villous growth of the bladder in a works where the men were engaged in handling aniline dyes made there. Dr. Legge's report of February, 1911, also states that

Dermatitis and eczema are produced by contact with several of the aniline colors—chrysoidin, Bismarck-brown, paranitranilin red, and others, but in none so markedly and so certainly as in the manufacture of dinitrochlorbenzene. In all the 16 cases referred to, dermatitis of the face, arms, armpits, and such parts of the body as are likely to be bathed in sweat, was the characteristic symptom, unaccompanied by any noticeable changes in the blood.

[8] The late Sir Henry Butlin, President of the Royal College of Surgeons, journeyed to the Continent expressly to ascertain the incidence of pitch-cancer at the briquette works. He returned with the information that the disease does not exist. Enquiry "through the trade" however, shows that it is about similar to the incidence in Great Britain.

PETROLEUM

There is no information that dermatitis or cancer is caused at the petroleum wells in America, Russia, or elsewhere; but absence of information does not necessarily mean that disease does not exist. At the shale oil[9] works in Scotland, however, paraffin dermatitis and cancer are not uncommon. Volkmann and Ogston's description, already quoted (see tar), also refers to the effects of paraffin. The two substances seem to produce very similar results. To judge from enquiry at the works, it is the crude paraffin which causes the trouble, and there have been some cases in the oil produced from cannel.

In his annual report, Dr. W. Walker, certifying surgeon for Mid Calder, states that during the year he has come across a few cases of "paraffin cancer" a disease from which shale oil workers are peculiarly liable to suffer, some more than others. It begins in a variety of forms, i.e., as an erythema, pimples, papules, etc.; these gradually dry, leaving hard crusts which, increasing in size, form hard, elevated, wart-like masses. As they increase in size these break down, and produce sloughing ulcers or paraffin cancers. He mentions three cases: (1) On the dorsum of foot, doing well after operation; (2) scrotal, so far doing well after extensive operation; and (3) back of wrist, necessitating amputation of the right arm at the shoulder. Enquiry by Mr. Brown (Edinburgh) elicited the following information as to the process of refining, so far as it affects the material handled in the press house, and as to the effect on the skin.

The shale is heated in vertical retorts, the gas being condensed, and the ammoniacal liquor separated from the oil by gravitation. The crude oil is distilled by heating and blowing steam through it, the result of the distillation being known as "green oil." The green oil is treated with 2 per cent sulphuric acid, and afterwards, in another vessel with 1 per cent caustic soda. The green oil already treated is again distilled with steam and fractionated, giving "light oil," "intermediate," and "heavy oils," the latter oils containing paraffin. The

[9] Shale and cannel are forms of coal.

light oil is treated with sulphuric acid and caustic soda, and then distilled, the result being "burning oil" which is ready for use, and "intermediate oil," which is added to the intermediate oil already obtained by the previous distillation of the green oil. The "heavy oil" passes through pipes to the cooling sheds, and is pumped through ammonia freezers and filter presses, the residue, in the form of a sludge or scale, being conveyed by a worm screw to the floor of the hydraulic press house. The heavy oil from the filters is re-treated with sulphuric acid and caustic soda, and again distilled and separated into "intermediate oil" and "lubricating oil." All intermediate and lubricating oils are then passed through coolers, freezers, and filter presses, and the scale is conveyed to the floor of the hydraulic press house by worm screw. It is this scale which causes the eruption on the arms of the workers. The men shovel the scale on to canvas cloths, which are laid in layers on bogies, the ends and sides of the cloths being folded over and the pile placed under the hydraulic presses. The liquid oil is pressed out and returns to the process again. The paraffin scale remaining in the cloths is shaken by hand into a melting pot, and blown into trays in sweating houses where it is purified by slow heat. It is then treated with animal black and is finally converted into wax. The men in the hydraulic press houses wear canvas bibs and leg coverings, but their arms are bare to the shoulders, and in handling the cloths they cannot escape coming into contact with the scale. The eruption usually takes the form of small pimples or red blotches, and is not painful unless these develop into boils. I examined the arms of 10 men of whom five showed warts, pimples, or scars.

The higher fractions, such as paraffin wax and "liquid paraffin" seem to be harmless. Indeed, liquid paraffin is consumed internally in enormous quantities as a purgative, and since its introduction as such during the last ten years there has been no such marked increase in intestinal cancer as one would expect if this substance caused a predisposition to cancer like pitch or soot. The higher refining process therefore evidently removes some noxious constituent.

Crude shale oil from some mines evidently cause more trouble than that from other mines, for several cases are reported from certain districts and none from others.

At the International Congress of Medicine in London, in 1912, Dr. Norman Walker showed some beau iful casts of paraffin dermatitis and epithelioma.

VASELINE

This is a petroleum fraction. It is used extensively on the skin to aid healing, and is said to increase the cell proliferation of healing.

GREASE

The manufacture of grease causes complaints similar to those produced by tar, but it requires no special comment here because they are evidently due to the tar oils which form a large constituent of commercial grease. Dr. Legge examined 31 men at grease works and found 6 suffering from pitch warts and 13 who had signs of old ones.

KANGRI CANCER

The "fire pot" is a wicker brazier having an earthenware center used by the natives in certain parts of India. It is carried inside the garments, as a rule suspended by straps over the shoulders. The fuel usually consists of decayed vegetable matter which forms a charcoal. The continual rubbing of this charcoal against the skin of the abdomen and thighs gives rise to thickening, ulceration, and epithelioma of the skin in much the same way as coal-soot and pitch.

TOBACCO

Smokers' cancer of the lip is generally associated with mechanical injury caused by the rough stems of clay pipes, and the incidence is less than it was owing, apparently, to the introduction of vulcanite stems; but mechanical injury will not account for the high incidence of malignant disease of the larynx and fauces of men as compared with that of women, in whom this disease is rare. Tobacco, as it is smoked, consists of the partially dried leaf which has been allowed to ferment by putre-

faction. It is frequently mixed with olive oil (a substance which causes dermatitis in several trades), and is sold damped to various degrees with water. The drier the tobacco the more the smoke is inclined to "burn" the tongue.

BETEL NUT

The so-called betel nut that is chewed by natives in Madras, Ceylon, and the Straits Settlements is a mixture of betel nut, tobacco, and spices, which is allowed to remain in a warm place until it becomes putrid. It is the cause of epithelioma in the floor of the mouth.

X-RAYS AND RADIUM RAYS

Radiation need only be mentioned here as causing burns of an intractable nature. They lead to ulceration which is liable to malignant infiltration. So much has been writtten on this subject, that passing mention only need be made.

ARSENIC CANCER

Pye-Smith (3) has recently published a collection of 31 cases of this disease, giving an accurate description of each. He points out that in nearly all cases of arsenic cancer

> It looks as if arsenic induces keratosis of the skin (as is now universally admitted), the keratosis mechanically inducing fissures, which readily become infected with bacteria and then ulcerate, the ulcers finally becoming cancerous.

He also suggests that arsenic may predispose the tissues generally towards cancer, a predisposition comparable to or even more marked than that caused by senescence; but it may be remembered that arsenic is a powerful cell-poison, and it may therefore bring about a result similar to that produced by old age, by causing cell-death.

It has been suggested that pitch cancer may be due to arsenic in the pitch. Tests made in these laboratories, however, have

failed to detect any arsenic in pitch. The pitch used at the briquette works has been raised to a temperature of 300°C. before it is consigned there. The same remark applies to the suggestion that pitch cancer is due to turpentine. There is no turpentine in tar, pitch, or soot.

LEUCODERMA, KERATOSIS, AND CANCER

Lenthal Cheatle has drawn attention to the frequent incidence of malignant infiltration supervening on patches of atrophic skin which have become subsequently thickened. These areas may even be bilateral, and may in the first instance be caused by nerve disease. As in arsenic cancer, there seems to be a local destruction of cells followed by proliferation, which may ulcerate and ultimately become cancerous.

FOUL ULCERS

Old untreated varicose or syphilitic ulcers are prone to become malignant, as is well known. Since there are no figures available, it is difficult to ascertain with certainty whether the degree of suppuration does or does not increase this liability; but it seems common experience to find the malignant infiltration in the more neglected cases.

MANURE

Senile warts occur on the hands and arms of farm laborers who frequently handle manure. The Registrar-General's returns for 1890–1892 show an incidence of 84 deaths as against 51 for all occupied males. In Germany agricultural laborers are especially subject to skin cancer.

When the foregoing commodities are examined collectively it becomes more apparent that mechanical injury per se can play only a minor part in the predisposition to occupational cancer. Apart from the evidence in this respect given by the coal-tar industries, the action of petroleum, arsenic, manure, tobacco, etc., also demonstrates it; for some of these commodities are solids, some are liquids, and physically they differ a great deal

in other respects. Yet they all seem to bring about the predisposition to malignancy in a somewhat similar manner, namely, by becoming impacted in the tissues, where, by giving rise to cell proliferation, they produce a warty condition. The warts usually ulcerate at their bases and drop off, leaving an intractable sore. It seems to be the edges of the ulcers that become epitheliomatous, and there appears to be a specific liability, when the industrial warts are untreated, for this to happen.

Mechanical trauma, it is true, will predispose the tissues to malignancy, both carcinoma and sarcoma, a fact proved by clinical experience and by experiments on animals; but in occupational cancer it is clear that a chemical factor is also concerned which acts directly on the tissues, in the first instance inducing cell proliferation. If it were not so, apart from the evidence enumerated above, we should expect to find a similar incidence among chimney-sweeps and briquette makers as among stone-masons and metal-grinders, who work with even more gritty commodities, and yet who do not specially suffer. There must be a chemical factor responsible and the question is, what is it? It is true that x-ray cancer and the predisposition caused by scars, keloid, and degenerate nerve areas may be initially due to mechanical trauma, that is to say, to excessive energy or heat, or destruction following upon deficient blood supply, etc.; but these factors are not sufficient to account for the incidence of occupational cancer, and it is possible that the initial trauma in x-ray cases may also be followed by some specific chemical change in the tissues.

In conclusion, one further point may be mentioned. When the active commodities are examined collectively, it will be seen that all of them, with one exception, are products of, or are derived from, the products of the death and decomposition of living matter, although such death may have occurred centuries previously. Coal and its derivatives, including paraffins, charcoal, tobacco, betel nut, and manure, all have such a derivation; the one exception is arsenic, and that, being a powerful cell-poison, may possibly produce the products of cell death and decomposition in the tissues. It is important to bear this in

mind, although there is no actual proof that such products predispose the tissues to epithelioma; yet it is a striking point, for these commodities undoubtedly cause this predisposition when impacted for a long time in the tissues of the skin, whereas inorganic commodities, such as stone-dust and metal-dust, are ineffective. In this connection, it is useful to remember that carcinoma seems more frequent, in general, at sites which are continually subjected to organic matter undergoing bacterial decomposition, such as the rectum, stomach and indeed the whole intestinal tract), mouth, uterine cervix, breast (chiefly in women who have borne children), prepuce, anus, scrotum, etc. In sarcoma, on the other hand, this does not apply, any more than does the age incidence; but with occupational epithelioma especially, given that the predisposing cause of the disease is present equally in different parts of the body, it is usually in that part which is the dirtiest or which is affected with open ulceration that the malignant condition supervenes.

Decaying organic matter of all descriptions fertilizes living matter, and promotes cell proliferation, being used extensively for the growing of plants in agriculture. Up to a certain point, the more putrid the matter, the more pronounced is this fertilizing property. Soot is used by gardeners for this purpose, but it is only useful when it is wet, showing that it is necessary to dissolve something out of it, namely nitrogenous compounds. Mere grit has not this action. Ammoniacal liquor distilled from tar is a very valuable commodity, owing to the nitrogenous compounds it contains, being converted into artificial manures. The trade in nitrates for fertilization is enormous. Soot and tar products, in causing the cell proliferation leading to warts, would seem to act in accord with this principle, and epithelioma itself is also a growth consisting of an excessive cell proliferation.

To sum up: There seems to be some specific *chemical* agent responsible for occupational cancer; *mechanical* irritation plays only a minor rôle in this disease; and lastly, there is a probability that the mischievous agents are organic nitrogenous substances of a group common to all the dangerous commodities. In the coal-carbonisation—commodities, the fact that the coal is bituminous seems to be essential.

PART II

If one were to attempt to isolate a substance or a chemical grouping common to them all from the many and complex commodities that give rise to occupational cancer, one would be faced with a problem so vast that it would be futile to undertake it. The coal-tar derivatives alone would present an insuperable problem, for they contain a large number of substances of many varieties, including nitrogenous bodies of several descriptions. Besides, there would be nothing to go upon; one would not have the faintest idea how to start. One might fractionate gas-tar, pitch, or soot, but even then one would probably hit upon the wrong fraction and it would be impossible to correlate such a chemical analysis with a subsequent one made on tobacco-smoke, betel nut, manure, and any various compounds of arsenic which may in some way be produced by the drug in the living tissues. It may be remembered that arsenic is a "cumulative" drug.

After consideration it was resolved to attack the question from a point of view based on a working hypothesis. It is admitted that this principle of making facts—such as those given in the first part of this paper—harmonise with even a working hypothesis is illogical; but there was no alternative. The only way was to choose a reasonable line of argument, keeping all the facts known about occupational cancer and cancer in general always in view, and then to proceed experimentally.

First the facts known about cancer in general were reviewed, and then the more acceptable of the several theories and working hypotheses were studied to see how far they could be made use of in the investigation of occupational cancer. Some of the facts have already been alluded to in the first part of this paper, e.g., the remarkable age incidence of carcinoma (the form of disease with which we are immediately dealing), the common sites, the question of chronic mechanical irritation, and above all the phenomenon of excessive cell-proliferation which is a characteristic of malignant disease. But two other facts were also kept prominently in view, namely, the propensity

on the part of the cells to infiltrate surrounding tissues, and the extraordinary fact that if the disease remains untreated the subject of it emaciates and dies for some reason that has never been satisfactorily explained.

The clinical data given in the first part of this paper undoubtedly justify the conclusion that, when dealing with the cause of occupational cancer, we are in reality concerned with two factors—a *predisposing* cause and an *exciting* one. The predisposing cause is evidently a chemical derived from the commodities when impacted in the tissues, but the exciting cause seems only to appear when ulceration has occurred, especially if the ulceration occurs in the dirtier parts of the body.

The term ulceration, when used in this sense, is not a very satisfactory one, for, although the classic definition "solution of continuity of surface" seems always to hold good before the site becomes malignant, the epitheliomatous condition invariably appears at the growing (cell-proliferative) edge where there may be no immediate loss of surface continuity, and the demarcation between the benign and malignant proliferation may not be clearly defined.

But there is a predisposing cause and an exciting cause undoubtedly at work before a case of occupational cancer becomes truly malignant. The specific commodity impacted in the tissue giving rise to cell-proliferation like a wart; sloughing, leading to ulceration; more cell-proliferation at the edge with ultimate infiltration, metastasis, and death. A definite sequence of events.

On the face of these facts, therefore, the older theories did not help very much. Take for instance the general hypothesis that cancer follows on chronic irritation, in favor of which there is considerable evidence. Let us analyse the expression "chronic irritation." An irritant must be either mechanical or chemical; a mechanical irritant must be due either to pressure or heat, or to both. The hot stem of a clay pipe is an example; an ill-fitting boot causing a corn which may become epitheliomatous is another. What happens to the individual living cell in the tissue which is subject to mechanical irritation? The term

"irritation" really is a clinical one; it has not a precise meaning to the cytologist. To the clinician the word implies a degree of injury as evinced by some reaction such as inflammation, pain, or itching, but there is no means of measuring the amount of injury suffered by the individual cell. Chronic irritation in a tissue is a definite condition, but when we discuss the individual living cell we had better use the generality—injury. "Injury," surely, is the right word, because both heat and energy, if present in excess, will ultimately produce damage and even death (destruction) in a tissue. Irritation is merely a degree of this injury. So it must be with the individual cell. The cause of the irritation, as it increases, must sooner or later first damage and then kill the individual cells which constitute the tissue and which cannot run away. It is submitted, therefore, that when we speak of chronic mechanical irritation in a tissue, we are in reality dealing with a population of cells, some of which are normal, some damaged, and some dead, according to the degree of injury. If the chronic irritation is slight, there may be no death rate above the normal, but there may be damage to a certain number of cells. Presumably damage to a cell means death of portions of its protoplasm. The pathological term "degenerate cell" usually means vacuolation when it is examined intra-vitam.

A chemical irritant seems to fall into a similar category. Chemical irritants, if their administration is pressed, sooner or later become destructive agents. The word "irritation" here again means a degree of injury caused to the tissue by the irritant, namely damage or death to the individual cells as the case may be. If a substance is an "irritant" in certain dosage, it must become poisonous in greater dosage. A given chemical in given dosage can only have one of three actions on the living cell; it may be beneficial, inert, or injurious, i.e., poisonous. The chemical irritant must be a degree of the poisonous variety.

As regards *mechanical* irritation: The first part of this paper has shown conclusively that mechanical irritation per se cannot be responsible for occupational cancer; the coal-tar commodities alone prove the point. A specific chemical is concerned without

doubt. Is this chemical an irritant? is the next question. Obviously not, for it produces cell-proliferation, not destruction in the tissue.

Moreover, if occupational cancer were entirely due to chemical *poisons* derived from the commodities, we should certainly expect, for instance, a greater incidence of the disease among those who handle the lighter fractions of coal distillation, especially the phenol, creosote, and naphthalene fractions, than among those who handle tar or pitch. But these lighter fractions, although cell-poisons, are harmless as far as the predisposition to cancer is concerned. A striking contrast to the non-poisonous soot. Surgeons and nurses, whose hands are frequently immersed in concentrated solutions of mercury biniodide do not suffer from cancer of the hands like those who are employed in handling paraffin at the shale works. Yet the mercury salt is infinitely more poisonous than anything contained in petroleum.

Trinitrotoluene and similar coal-tar derivatives used in munition manufacture, when impacted in the skin, cause dermatitis, and even atrophy of the liver, owing to their poisonous effects. Yet there has been no "flare" of squamous-cell epithelioma as a result of their action.

Nevertheless, apart altogether from occupational cancer, it must be admitted that chronic mechanical injury *does* give rise to a predisposition to malignancy, to wit—the clay pipe and the lip, the ill-fitting boot and the corn, the blow on the breast and scirrhus, the operation on the mole and melanotic sarcoma. Chemical injury also, in a similar manner, apart from occupational cancer, undoubtedly predisposes tissues to carcinoma, namely, chemical substances produced by inflammation as occurs in an erosion of the uterine cervix, syphilides of the tongue, etc.; these seem frequently to be due to chemical irritants of some degree.

But irritants are not nearly so powerful in their action as the occupational commodities. Neve, of the Kashmir Mission Hospital found 848 cases due to Kangri soot out of a total of 1189 squamous carcinomas. It is true that arsenic is a cell-

poison, and therefore might be classified among the "irritants," but the predisposition due to arsenic does not appear until years have elapsed after the patients have taken and have ceased to take the drug.

Injurious agents, therefore, both mechanical and chemical, by virtue of the degree of irritation they produce, by causing an amount of damage or death in the cell-population, may produce in a tissue a predisposition to cancer; but in occupational cancer something more is needed, namely a specific chemical which is contained in all the commodities themselves, and which sets up cell-proliferation (the wart) when impacted in the tissues.

The time honored hypothesis of Cohnheim does not harmonize with the clinical facts regarding occupational cancer. One could imagine, perhaps, that certain cells might retain a sort of quiescence from fetal days and then "light up" during senescence, although why these cell-rests, which are physiological components of the body, should ultimately destroy the patient, and incidentally themselves, is difficult to understand. One could even imagine that chronic mechanical injury might in some way cause the cell-rests to "light up," but it is impossible to believe that those who grind gas-tar pitch in Cardiff should have cells included from birth, while those who grind blast-furnace pitch in Whitehaven should enjoy immunity. Cohnheim's hypothesis drives us to this reductio ad absurdum.

The same argument applies to the suggestion of Farmer, Moore, and Walker, which is based on the Weismann hypothesis of inheritance, and which, like Cohnheim's, does not divide the cause of cancer into predisposing and exciting origins. It is by no means proved that the cells of vertebrates are separated into somatic and reproductive varieties, and, even if that were the case, it is not probable that Indians who use the Kangri fire-pot should have more reproductive cells in the skin than those who become covered with shoe-blacking.

Shattock and Dudgeon have lately sought to advance the question by attacking the cause of cell-proliferation. They have suggested that cells multiply instinctively unless restrained by an antibody, and that pathological variation in the antibody

may produce tumors, etc. An antitoxin for an instinct is decidedly new; but as a solution of the problem of growth, the very premises of this hypothesis have never been proved; on the contrary, some of the earlier experiments at Rothamsted Experimental Station have shown that plants, at least, become barren if they receive no chemical stimulus from without.

The work of Roger Williams is of more assistance, for, apart from the mass of information on cancer in general contained in his book, he draws a suggestion from it that the immediate nutrition of the cells may play a rôle in the causation of the disease. The conclusions arrived at in the first part of this paper appear to be somewhat in accord with this view.

On the whole, therefore, the well known hypotheses did not offer a firm standpoint on which to base a series of experiments. None of them offered any test to which the several commodities that cause occupational cancer could be subjected. So it was considered better to proceed on lines of work in which the writer had been engaged for several years, investigating the causes of cell proliferation. As pointed out in the first part of this paper, cell proliferation is the first and a constant result of the action of all the commodities which give rise to occupational cancer.

This working hypothesis was based on a series of experiments which has produced evidence that, so far as certain groups of cells at least are concerned, their division is due not merely to instinct on the part of the cells themselves but to specific chemical agents, all of which appear to be amino substances set free by cell-death. According to this hypothesis cells divide in response to this *stimulus* from without; that is to say, the reproduction of cells is initially prompted by death occurring among their neighbours, cell-death setting free the amino substances, and the latter exciting cell-division among the surviving cells.

The hypothesis arose in 1909 from research with the jelly method of in vitro staining, by which it was found that cell-division can be induced in living human lymphocytes by mixing watery extracts of dead tissues with the jellies on which the individuals cells are resting. Subsequently the extracts were made to induce division in leucocytes and certain epithelial cells also.

Improvement in the test revealed the fact that the active agents in the watery extracts were nitrogenous substances produced by the decomposition of proteins, and several were isolated and proved to consist, among others, of some of the purin bases, such as creatin, xanthin, and tyrosin. For convenience the name *auxetic*[10] was given to these cell-division-producing agents.

The action of auxetics on blood-cells was confirmed by R. Ross and again by Drew. Fantham succeeded in inducing division by auxetics in individual *Entamoeba coli*, the writer in the ova of *Ascaris megalocephala*, Drew in the spores of *Polytoma granulosa*, and in a fine series of experiments Cropper and Drew (4) have found that amoebae increase enormously in numbers in response to auxetics. Indeed the last authors have found that when individual amoebae are isolated from all other living creatures and placed in distilled water or on jelly containing only distilled water, they will not divide at all unless an auxetic be present, that auxetics will up to a certain point increase their proliferation according to the strength of solution, but that after a few generations have passed the presence of a ferment is also necessary if proliferation is to be kept up.

With these various classes of cells, then, auxetics undoubtedly prompt proliferation. When first the experiments with human white blood cells were published, it was disputed that the figures induced in lymphocytes were those of cell-division, because the jelly method revealed the fact that these figures, although they were in general principle those of mitosis, as far as lymphocytes are concerned, were dissimilar as regards what is generally believed to be the nucleus. But estimations of increase in numbers by precise methods, together with the work of Cropper and Drew and others, seem to settle this point, for the cell-division which they induce in amoebae is of the normal type.[11]

Since certain human and some other cells will divide in re-

[10] The name implies an excitor, which in its turn may and has been interpreted to mean a stimulant; but it is debatable whether they are such or whether they are foods. Without doubt, some are foods.

[11] Cropper and Drew's work has recently been confirmed by H. G. Thornton and Geoffrey Smith using *Euglena viridis*. Proc. Roy. Soc., Series B, London, 1915, lxxxviii, 151.

sponse to auxetics, and since these auxetics are produced in a tissue by cell-death, the working hypothesis was extended to cell-proliferation which is frequently the predisposing cause of cancer. Injury gives rise to cytolysis and to the cell-proliferation of healing, and if it becomes chronic, proliferation to the extent of production of benign tumor formation may be brought about. In order to test the last point, auxetics were introduced into the mammary ducts of goats' breasts—using a blunt hollow needle to prevent injury—and adenomatous nodules were produced.

The working hypothesis, therefore, had a basis founded on experimental facts. Cells had been made to proliferate both in vitro and in vivo by means of auxetics. Healing of a damaged site presumably is brought about by auxetics set free by the injurious agent, the amount of proliferation being in ratio to the amount of damage, a theory which seems to be a reasonable one.

Some preliminary experiments were then made with soot and with gasworks and blast-furnace pitch. Using living human lymphocytes as the test cells and employing the jelly method, it was possible to detect auxetics in the soot and gasworks pitch, but only to a very slight degree, if at all, in most varieties of blast-furnace pitch. Later on, H. Bayon succeeded in producing a condition resembling the early stages of squamous epithelioma in rabbits' ears by injecting watery extracts of gasworks tar and pitch. Similar extracts of blast-furnace pitch, on the other hand, used in a similar way, did not produce this result.

The jelly method further showed that most of the alkaloids excited amoeboid movements in leucocytes and some forms of epithelial cells, an observation originally made by Osler, and the term *kinetic* was given to such substances. It was found that many kinetics, although they do not themselves induce cell-division, have a power of augmenting the action of auxetics in doing so. If an auxetic is present, the addition of a kinetic may increase the action of the auxetic as much as five fold, as can be measured by the quantity of auxetic present. Choline and

cadaverine (pentamethylene diamene), products of putrefaction, are powerful augmentors as well as kinetics, acting in this way like the alkaloids.

All the occupational commodities were then tested for auxetics and kinetics, and some of them for augmenting the former. The cells used were human lymphocytes for auxetic and augmentor, and human leucocytes for kinetic action.[12]

SOOT

A 20 per cent watery extract contains both auxetics and kinetics.

BLAST-FURNACE PITCH

A 10 per cent watery extract contained a trace of kinetic only, and auxetic could only be detected if this action were artificially augmented by an alkaloid such as atropine.

GAS-WORKS PITCH

A 10 per cent watery extract contained both auxetics and kinetics.

GAS-TAR

A 10 per cent watery extract contained both auxetics and kinetics.

BLAST-FURNACE TAR

A 10 per cent watery extract contained no auxetic or kinetic.

There is, then, an experimental difference between blast-furnace tar and pitch and the ordinary gas-works varieties, which is in accordance with the clinical evidence. As already stated, there are two explanations for this difference, one being that blast-furnace tar (and therefore the pitch) is chiefly derived from the less bituminous Scottish coal, the other being that it is pro-

[12] A complete description of the experiments together with the technique will be found in the Brit. Med. Jour., 1911, 1, 884, and 1913, 1, 511; and in Researches into Induced Cell-reproduction and Cancer, vols. I–III, (London and Philadelphia), 1911 and 1913.

duced at a lower temperature. Samples of coal from various seams were therefore tested. They were sent to the laboratory distinguished by numerals only, the key being kept at the Mines Department of the Home Office until the tests were complete. It was found that coal does not contain nearly so much auxetic or kinetic as do tar, pitch, or soot. High concentrations had to be made in the extracts (ten times higher than tar) before any action could be detected; and the more bituminous coals contained auxetics and kinetics, while the harder varieties contained only traces or none at all. This seems to be the explanation why blast-furnace tar and pitch contain less auxetics and kinetics. From this time onwards all experiments were of the "blind" variety.

In order to control the foregoing experiments, and to ascertain which fractions of tar are responsible for the auxetics and kinetics, a series of experiments was made with thirty-two samples of tar, pitch, and various oil fractions derived from them. The difference between blast-furnace tar and pitch and the gas-works varieties was again detected, and it was demonstrated that the auxetics and kinetics are contained in the middle fractions of tar. The lighter oils, such as the naphthalene and creosote fractions, are free. It was also found that the auxetics in tar become volatile at about 350°C.

These facts correspond with the theory at the works that the mischievous elements are in the anthracene fraction, but since anthracene itself is not an auxetic, it is evident that the auxetics are impurities in that fraction.

Mrs. Norris, working in these laboratories, has recently been able to isolate two auxetics from tar. One is a substance apparently identical with pseudocumidine, which is only a feeble auxetic, the other is an active base, having an empirical formula $C_{22}H_{14}O_9N_6$, but nothing is known as to its constitutional formula.[13]

Hence the auxetic and kinetic content of tar and its derivatives seems to harmonize with the incidence of the disease

[13] Note on the bases of gasworks coal-tar which are believed to be the predisposing cause of pitch cancer with special reference to their action on lymphocytes together with a method for their inactivation. Biochem. Jour., 1914, viii, 253.

caused by these commodities; the more concentrated they become, the more auxetic and kinetic they contain up to a certain point when the auxetics become volatile. Unfortunately this point, 350°C., is too high for a serviceable pitch to be prepared, or the problem at the briquette works would appear to have a simple solution. Such a pitch is too hard and contains too much carbon for it to be used as a binder for briquettes, and its calorific value is greatly reduced. The auxetics, being soluble, can be washed from the tar, but this also was objected to by the trade because of difficulty in removing water from tar. Its presence causes deterioration of the pitch and danger from explosion during distillation.

OTHER TAR PRODUCTS

Certain tar antiseptics contain auxetics, and some of the capsules advertised for internal administration also have this action.

Naphthalene, which is converted into the harmless shoe-blacking, has not this action.

PETROLEUM

Some samples of commercial refined paraffin oil (kerosene) contain auxetics, and vaseline also has this action. A series of "interim oil scales" and heavy lubricating oil fractions from Oakbank, Addiwell, and Broxburn, in Scotland have been tested. None of them apparently contain auxetics, but four out of seven contain kinetics, and three out of the four kinetic samples are also augmentors.

TOBACCO

Tobacco contains auxetics. Ten per cent watery extracts of ordinary pipe tobacco showed this action to a considerable degree, many cells exhibiting division figures when the 10 cc. of jelly contained 1 cc. of the extract. The water in a "hubble bubble" pipe, through which tobacco smoke had been drawn from 50 grams of several forms of prepared tobacco, also gave an auxetic reaction, but a watery extract of a cigar did not appear so active, it requiring a greater strength of extract.

ARSENIC

Soon after kinetic action was first observed with the jelly method, it was found that arsenic salts in some strengths excited amoeboid movements in leucocytes, and Pye-Smith's recent investigations have prompted more experiments with them. Like the heavy petroleum fractions, certain arsenic compounds are not auxetics, but some of them are augmentors when added to organic auxetics. Arsenic oxide, salvarsan, atoxyl, and sodium arseniate are all kinetics, the first being the most active, the last the least. When extracts of meat were used as the auxetic, the first three compounds proved to be augmentors in the order named as regards strength, but the sodium salt was negative. The jelly on which the cells were spread required at least 3 cc. of a 1 per cent solution of the arsenic compound to produce this augmenting action. But no such action occurred with an artificial auxetic such as theobromine.

By itself, then, arsenic does not appear to produce cell proliferation, but in the presence of products of cell death—such as the extract of meat used in the experiments— it augments the action of the auxetics contained therein. It is possible that chronic skin eruptions due to arsenic are caused by this action. The oxide is the most active salt in vitro, but there is no evidence as to the combination in which the drug is held in the living tissues.

ANILINE DYES

Many of these, especially methylene blue, azure I and II, eosin, neutral red, etc, have an auxetic action on blood cells in vitro, and when injected into tissues in vivo also produce cell proliferation. In view of the fact that their chemical constitutions are so different, it is probable that they produce this action by causing cell death in the first instance, the cell death in its turn setting free auxetics. Cells will live with their granules stained, but their death occurs as soon as the intranuclear chromatin is reached by the stain.

MANURE, PUTRID WOOD CHARCOAL, PRODUCTS OF SUPPURATION IN ULCERS

These all come into one category. Auxetics can be detected in decaying organic matter, and, if the putrefaction has progressed, kinetics with augmentation are also present. Drew has recently tested pond water for these actions, and has found them increased after the cell death of the winter, suggesting that they are responsible for the awakening of pond life in the spring. There seems to be a relationship between the content of auxetics and albuminoid ammonia. It was with a putrid extract of a dead tissue that cell division was first induced in lymphocytes in 1909. But if the putrefaction has progressed beyond a certain degree, poisonous substances are produced which cause cell death.

Experimentally, therefore, the action of the commodities can be explained by the auxetics or augmentors contained in the commodities themselves. They become impacted in the tissues, either in the hair follicles or the sebaceous glands, or perhaps in fissures caused by slight mechanical injury. Auxetics are dissolved out of the commodities and set up cell-proliferation, giving rise to thickening and warts. The warts slough and drop off, leaving an open ulcer, in which the over-prolific cells at the edge are prone to become malignant. The malignant invasion, judging by clinical evidence, seems to be due to some additional factor, possibly connected with production of more kinetics, which excite amoeboid movement and still further augment the proliferation. From the clinical evidence in occupational cancer, the additional factor appears to come from without. The apparent necessity for open ulceration, and the fact that it is the dirtier parts of the skin which are more liable to the disease, are points worthy of consideration, although the suggestion is as yet entirely theoretical and there is no absolute proof that it is correct.

Auxetics are produced as age advances, the physiological increase of cell death during senescence having this result. It is part of the working hypothesis that the predisposition to cancer

during senescence may be due to a predisposition to cell proliferation caused by auxetics physiologically free in the tissues in general. And, as already pointed out, so may it be with mechanical and chemical injury; the predisposition to cancer brought about by them may also be due to the auxetics set free locally by the trauma. But in occupational cancer, in addition to the auxetics produced by any mechanical or chemical trauma, there are also those contained in the commodities themselves which would produce, and which actually seem to produce, a greatly increased if not a specific predisposition.

The unsatisfactory part of the above work, however, is that it is based on a working hypothesis. There is always a danger, when working in this way, of being biased in favor of a hypothesis; but in this case there was no alternative, and all the experiments were "blind" ones. Since one cannot distinguish by appearance between varieties of tar, pitch, and oils, the experimenters had no idea which was under investigation at any given time; and it is remarkable how accurately the results of the experiments harmonized with the clinical facts. Still, when elaborating such a hypothesis, even though, as in the case in point, it is based on direct experimental evidence, great care must be exercised to prove each step. In the cancer problem, unfortunately, this is not easy, for it involves so many other problems; e.g., the cause of the reproduction of living matter, of development, metastasis, of death, etc., about which very little is known, so that, at present, as regards occupational cancer, one can only work on the somewhat empirical lines described in this paper.

It should be remembered, therefore, that although there is experimental proof that auxetics stimulate the proliferation of cells, a gap is jumped if we assert that they predispose a tissue to cancer, for there is no definite proof of this. It is true that by auxetics cells may be made to divide when removed from the body; and it is true that auxetics, when artificially inoculated into animals, will produce proliferation amounting to benign tumors, and if continued with augmentation will produce a condition identical in microscopic appearance with epithelioma.

It is also true that benign tumors, in a wide sense, form a predisposing site for cancer, and equally true that the auxetic theory coincides with the clinical evidence. But we cannot assert that this is the way in which the predisposition is caused naturally in the living tissues. Proof cannot be obtained owing to lack of methods. The jelly method enables us to test the action of chemical substances on individual living cells in vitro; Carrel and Burroughs have shown how to grow cells in tissue formation in vitro; and sectioning will show the arrangement of cells after death. But there is no method by which we can see with chemical-detecting eyes, so to speak, into a living tissue in its natural surroundings. Therefore we cannot see whether, or how, auxetics work, except under experimental conditions.

An effort is being made, however, to prove the auxetic theory by destroying those substances in tar on a large scale, and observing whether this destruction prevents the incidence of warts and cancer at the briquette works. Mr. H. W. Robinson, of Messrs. Robinson Brothers, tar distillers, West Bromwich, has suggested that the application of the Sorensen reaction might be practicable. Formaldehyde inactivates amino substances, and tests have proved that it destroys the auxetics in tar. Three years ago this was tried on a considerable scale Messrs. Bird and Son, Cardiff, prepared a large quantity of pitch made from tar treated with formalin, and this pitch was used exclusively at one briquette mill of the Crown Preserved Fuel Company at Cardiff. It was originally intended for this experiment to continue for six months, but unfortunately, owing to unforeseen circumstances, a mechanical breakdown occurred at the tar-distilling works, and the experiment came to an end in two months. The time was too short for the medical commission, who were nominated by the Home Office, and who had previously examined the men's skin, to offer an opinion on the result. The war then broke out, and the shortage of formaldehyde prevented a resumption of the experiment. But the government has promised to undertake it anew as soon as possible, and it is to be hoped that it will then be carried out on a larger scale, the whole of one briquette works to use nothing

but treated pitch for one year (about 50,000 tons) and the other works to act as controls.

If the destruction of auxetics in tar leads to the prevention of occupational cancer at the briquette works, it would appear that the case against auxetics is established.

POSTSCRIPT

Since this paper was written, the writer has seen an excellent paper by Dr. Walter J. Heiman in the Journal of Cancer Research, 1916, i, 343, on "Precancerous dermatoses." It complains that the expression "precancerous" is misleading. True, the term is wrong; as Dr. Heiman points out it implies a constant forerunner of cancer. But the expression is not common in Great Britain, and the writer never heard it mentioned in the United States seven years ago.

As was mentioned in the discussion of chronic irritation, many lesions, whether caused by physical force (mechanical injury) or by chemical action (poison), undoubtedly lead to cancer, some occasionally, some more frequently; but it does not necessarily follow that every mechanical or physical trauma is always followed by cancer. Especially in medicine, one can take stock phrases too literally. "Predisposing" seems to be a better term than "precancerous," implying as it does liability, or a more frequent occurrence than usual.

It seems probable, therefore, that the majority of the dermatoses and conditions to which he refers are probably the result of chronic injury (mechanical or chemical) and might be classified as such; but the more occupational predisposition, as already shown, falls into a different category from a clinical point of view, in that a malignant outcome is more constant and the commodities themselves contain or produce a definite predisposing agent.

Kangri cancer is not due to burns only, as Dr. Heiman assumes, but also to the remarkable form of soot which is rubbed into the burn. It is not a little dangerous for Dr. Heiman to draw deductions from his thirteen cases, for the Pearson-Poisson

formula would show a large error of random sampling. But when he states that "we lack a control, a standard of comparison" he strikes a true note, which the writer thinks applies to many issues in cancer research.

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MULTIPLE SKIN METASTASES FROM CANCER OF INTERNAL ORGANS[1]

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INTRODUCTION

In cancer of the internal organs, metastasis into the skin is so rare that Gurlt observed not a single case among 16,637 patients, and neither Reichelmann (711 cases), nor Gussenbauer and Winiwarter (903 cases of gastric cancer), mentioned the occurrence of secondary tumors in the skin. Redlich, Heimann, and Krasting, however, recorded 2 cases out of 496, 2 out of 20,000, and 2 out of 12,730 patients respectively, Lex 7 out of 1183, and Mielecki 3 out of 487 cases. Daus collected 38, Sudo 72, and Kaufmann and Wolf 78 cases from the literature and from among their own patients.

The present paper is an analysis of 110 cases which the writer has collected from the literature, to which are added 5 cases that have come under his own observation. One of the 5 was very kindly brought to his attention by Dr. Hojo.

THE AUTHOR'S OWN CASES

The fragments examined were taken from various organs which had been preserved in alcohol after formalin fixation, and stained with hematoxylin and eosin, Van Giesen's stain, or when necessary, by Mallory's, Bielshowsky's, or Weigert's (elastic fiber) method.

[1] The author has not read the proof of this article.

Case I. M. M., farmer, forty-six years old

Status præsens. There is a tumor on the right side of the neck about half the diameter of the palm, and multiple nodules in the integument of the chest and back; these are of various sizes, bluish, indistinctly defined, flat, firm, painless, and freely movable. The cervical and submaxillary lymph-nodes are not palpable, but those of both inguinal regions and both axillae, particularly the latter, are enlarged and firm. The entire body, especially the lower limbs, is very edematous. There are no other findings of importance.

Autopsy findings. Well nourished male of large frame; general edema.

Skin. There is a hard flat tumor of irregular and indistinct outline, about half a hand's breadth in diameter, on the right side of the neck. In the integument overlying the front and lateral regions of the chest and the upper half of the back, there are nodules varying in size from a hazel-nut to a child's palm; in the epigastric region there is one about the size of a small peach, while a little below the right costal arch there lies still another, this one about the diameter of a hazel-nut, flat, irregular in shape and indistinctly defined.

Many lymph-nodes in both axillae and both inguinal regions (especially on the left side) are enlarged, varying from the size of a bean to that of a sparrow's egg. A number of the bronchial nodes are equally involved, but those of the cervical and supraclavicular regions are not so much affected.

Suprarenals. Around the left one the connective tissue is greatly increased, and the gland has increased to the size of a hen's egg.

Stomach. At the lesser curvature especially there is a distinct cancerous change and in the middle of this curvature a small shallow ulcer. The cardiac end and the lower part of the esophagus are involved by some slight cancerous infiltration, but in the pylorus and the other parts there is no pathological change worthy of note.

Duodenum and small intestine. Negative.

Large intestine. There is a hard tumor about the size of a bean in the upper part of the sigmoid flexure.

Mesentery. Many mesenteric lymph-nodes are swollen to the size of a hazel-nut or a pea. In the middle of the small intestine there is a hard thickening 3 cm. in diameter, nearly round in shape, with a center about two finger-breadths from the intestinal canal. Its margin is formed by fat, and the thickening itself presents a radiating structure like a chrysanthemum.

Retroperitoneal lymph-nodes. Not greatly enlarged.

Microscopical examination. Stomach. Carcinomatous ulcer of the lesser curvature, invading the muscular layer, the subserous connective tissue, the lymph-channels, and the blood-vessels.

Skin. The epithelium is normal. In the corium and the subcutaneous stratum the connective tissue is greatly increased, and cancer cells are embedded in it singly or in groups. Hair-follicles, sebaceous glands, and the region around them show no pathological change, but cancer cells are to be seen about the sweat glands, some of which show traces of atrophy. There are cancer cells in the lymph-vessels here and there, but none are visible in the blood-vessels. The corium and the subcutaneous layer show a great increase of the lattice-fibers in addition to a distinct increase of the collagenous fibrils, especially around the sweat glands. Where the cancer cells lie in groups, the lattice-fibers surround every cancer cell like the strands of a net.

Suprarenals. Cancerous infiltration.

Lymph-nodes. Mesenteric, retroperitoneal, bronchial, both axillary, cervical, inguinal, and supraclavicular groups infiltrated by cancer cells; increase of connective tissue, and infiltration by eosinophiles.

In the blood-capillaries and small veins of the medulla of the left kidney and the submucous stratum of the bladder, and in the small arteries of the lung, emboli of cancer cells.

The cells of the metastatic growths have undergone mucous degeneration and contain small vacuoles. On account of these vacuoles, the cells are enlarged, their nuclei being pressed to the margin making them look like signet-rings. The cells in the chrysanthemum-shaped thickening in the mesentery contain particularly large nuclei (giant nuclei), some of them four or five times as large as those in the other metastatic growths.

Case II. N. N., forty-three years old

Status præsens. The skin and the mucous membranes are icteric. On the front and lateral parts of the chest and abdominal wall there are innumerable small hard tumors varying from the size of a hempseed to that of a pea, distinctly outlined, tender, and freely movable on the underlying tissues. Lymph-nodes not palpable. There is peristaltic unrest of the stomach. In the epigastric region it is possible to feel a resistance, but no tumor.

Autopsy findings. A medium-sized, delicately built, emaciated male.

Skin. Universally icteric. On the front and lateral parts of the trunk, and especially on the abdominal wall, there are innumerable tumors varying from the size of a millet seed to that of a sparrow's egg; these are hard, distinctly outlined, and freely movable.

Heart. Many small hard nodules under and in the serous membrane of both vestibules.

Lungs. Intact. Bronchial lymph-nodes not enlarged.

Great omentum and mesentery. Many small firm tumors in the neighborhood of the lesser and the greater curvatures of the stomach.

Kidneys. Multiple small hard tumors in the fat capsules of both kidneys.

Suprarenals. Both of normal size; a nodule about the size of a pea in the connective tissue around the left one.

Liver. Periportal lymph-nodes enlarged. Metastatic growths in the gall-bladder.

Stomach. The pyloric part contains an annular ulcerated swelling. In the anterior wall of the pylorus are many minute grayish white nodules.

Duodenum. Mucous membrane 1 cm. from the pyloric ring is firm and uneven.

Small intestine. Grayish white tumor the size of a lentil 50 cm. from its uppermost part. All along the small intestine there are about twelve similar growths, especially numerous at the ileocecal part.

Pancreas. Normal size, but very hard. Hemorrhage into the head of the organ; small tumor at the opposite extremity.

Retroperitoneum. Lymph-nodes enlarged and very hard, with a marrowy appearance on the cut surface. The fat 7 cm. below the ileocecal portion, the great omentum, ileocecal fold, transverse mesocolon, and pancreatico-gastric ligament contain many small firm nodules. Similar growths in the subperitoneal connective tissue of the diaphragm.

Prostate. Somewhat enlarged and shows on section metastatic knots which look marrowlike.

Microscopical examination. Stomach. The tumor at the pyloric end is an adenocarcinoma, which is invading the stomach wall and its small blood-vessels and lymph-channels. The lymph-nodes of the pyloric and cardiac regions are also involved.

Skin. Extension of the secondary growths by way of the lymphatics.

Heart. Metastatic carcinoma.

Lungs. Cancer cell embolus in a small bronchial artery of the right lung. The bronchial lymph-nodes contain metastatic cells only in the marginal lymph-sinus.

Liver. Many cancer cells in the lymph- and blood-capillaries of Glisson's capsule. Metastases in the wall of the gall-bladder, and cancer cell emboli in its smaller arteries.

Pancreas. Metastases only in the connective tissue septa; these contain a few giant cells.

Suprarenals. Metastases in medulla, cortex, and capsule.

Retroperitoneum. The tumors in the fat 7 cm. below the ileocecal region, the great omentum, the transverse mesocolon, the pancreatico-gastric ligament, and the subperitoneal connective tissue of the diaphragm, are metastatic adenocarcinomata. They are sharply defined and their cells are closely pressed together into solid masses; the amount of connective tissue is very small.

Prostate. Similar secondary growths.

Kidney. Cancer cells in the blood-capillaries and the small veins of the left kidney.

Retroperitoneal lymph-nodes. Metastatic adenocarcinoma.

Axillary and inguinal lymph-nodes. Not enlarged. Microscopically only a few cancer cells are to be observed in the marginal sinus of some of the inguinal nodes.

Case III. K. K., forty-four years old

Status præsens. Both lateral and posterior cervical lymph-nodes are enlarged. Axillary nodes firm, not tender, and about the size of a pigeon's egg.

In the epigastric region there is a tumor about the size of a hen's egg, which is freely movable and a little tender. In the integument of the abdomen many compact tumors, and they are not tender. They are as large as a pea and situated in the subcutaneous tissue.

Inguinal lymph-nodes. Both sides somewhat enlarged.

Autopsy findings. A middle-sized emaciated female.

Skin. In the subcutaneous tissue of the anterior part of the abdomen there are many firm movable tumors.

Great omentum. In the region of the stomach there is a number of firm grayish white nodules.

Peritoneum. Small soft white nodules.

Stomach. Form normal and size somewhat small. The serous membrane of the cardia is very uneven, and adherent to the diaphragm. The greater curvature is partially adherent to the transverse colon, and the pylorus and the lesser curvature to the pancreas and the retro-

peritoneal and periportal connective tissues. Over all the mucous membrane there are many small, flat, grayish white growths. The whole wall is thickened unevenly, and at the cardia it is especially annular, with its lumen so narrowed as to allow only rice-grains to pass through. In the pyloric region there are no localized pathological changes. The lower part of the esophagus and the duodenum near the pylorus contain small tumors.

Pancre . A number of growths, some as large as a pigeon's egg. Mesenteric, retroperitoneal, inguinal, and left axillary lymph-nodes enlarged.

Small intestine. There are from the beginning to the ileocecal region about 20 small round or elliptical submucous tumors, grayish white in color. In that part of it which is close to the ileocecal valve there is a transverse ulcer 2.0 to 3.5 cm. in width, with margins thickened like banks, and its ground is grayish white and shows many miliary growths. At the beginning of the cecum there are two small tumors.

Kidneys. Some small nodules are localized in the adipose tissue at the hilum of the left one.

Ovaries. In the left one, there are many small grayish white tumors. The right one consists of many rough knots.

Microscopical examination. Stomach. The wall of the cardia is very much thickened by an abundant increase of polygonal cells and connective tissue. Mostly adenocarcinoma, but some scirrhus. Muscular coat notably thickened. Between muscle bundles, cancer cells lie singly or in groups.

Skin. The metastatic tumors are situated particularly in the subcutaneous connective tissue, and are not sharply defined, so the cancer cells infiltrate into the connective tissue around the metastatic nodules and through the spaces between the fat cells or the fibers of connective tissue. The cancer cells are not arranged adenomatously, but singly or in groups. Some have swollen mucus thereby becoming "signet-ring cells." In certain parts the connective tissues are increased abundantly, and there is a scirrhous appearance here and there. In these metastases a number of giant-cells and cancer cells with the giant nuclei are to be found. The cancer cells also form metastases in both ovaries, small intestine (mucous and submucous connective tissue), mesentery, great omentum, and in the periportal, inguinal, axillary, retroperitoneal, and mesenteric lymph-nodes. The cancer cells are arranged adenomatously, singly, or in solid masses.

Case IV. H. O., sixty-one years old

Status præsens. Abdomen. Very much distended; the contour of the stomach is distinctly visible. At times a fist-sized, hard, contracted intestinal knot and a peristaltic movement are visible in the abdomen. The abdomen is tender all over when pressed, but there is no particular seat of pain, nor any hard circumscribed tumor palpable; on percussion somewhat tympanitic. No fluctuation is observed.

Autopsy findings. A middle-sized, large framed, emaciated male.

Skin. In the integument of the epigastrium there is a fresh wound, made by the extirpation of a metastatic tumor. In the subcutaneous tissue of the sacral region there is a tumor about the size of a large cherry.

Thorax. No mediastinal lymph-nodes are enlarged.

Liver. On the surface and on section there are many firm tumors, some as large as a pecan nut. A periportal lymph-node is enlarged to the size of a bean.

Rectum. Annular tumor the size of an egg, with ulcerated and uneven surface, about 4.5 cm. above the anus. By this tumor the lumen of the rectal canal is narrowed. At the upper part of the rectum, namely, the part corresponding in location to the bottom of the pelvic cavity, there is a perforation, large enough to allow the thumb to pass through. Other abdominal organs show no pathological change.

Lymph-nodes. Retroperitoneal, left supraclavicular, and both iliac-nodes, bean-sized, enlarged and somewhat hard.

Skull. Parts of the left temporal bone and of the sphenoid bone are softened. So the bone substance in these parts became lost, and there is a soft tissue in these places.

Microscopical examination. The tumor is an adenocarcinoma which has invaded the wall of the rectum.

Liver. The metastatic growths are generally adenocarcinoma. The cells are arranged in adenomatous structure, but at some parts are pressed closely together into solid masses; there is no increase of connective tissue.

Skin. The metastatic knots are situated in the subcutaneous tissue, and are not sharply defined. The cancer cells are arranged in adenomatous form but some groups have no lumen. There is a well developed stroma between these cancer cell masses.

Sphenoid bone. Metastases.

Retroperitoneal, periportal, and iliac lymph-nodes:—Metastases.

Case V. (*Courtesy of Dr. Hojo.*) *T. Y., forty-three years old*

Status præsens. The patient is a very emaciated man. In the stomach region a resistance is felt on palpation, and the patient feels a dull pain when the stomach region is pressed. The cervical, axillary, and inguinal lymph-nodes are enlarged from sparrow's to hen's egg size.

Subcutaneous tumors, varying in size from that of a bean to that of a hen's egg, are found scattered over the abdomen, shoulder and back, right thigh (internal aspect), lower part of leg (anterior aspect), and the sacral region.

Microscopical examination. (Nodules in the integument of the thorax and the thigh.) The tumors are located mostly in the subcutis, but the cancer cells have infiltrated continually into the corium. These cells are all polygonal, and arranged mostly in one layer, but some in many layers, so that they form narrow irregular lumina. Their nuclei and protoplasm can be stained distinctly. They seem to have no tunica propria.

Thus we were led to think that these were skin metastases of the adenocarcinoma and from the clinical symptoms the primary organ was perhaps the stomach.

SUMMARY OF PRECEDING FIVE CASES

To sum up these 5 cases of the skin metastases of the cancer:

a. Sex. Four of the cases were male, 1 being female.

b. Age. Four were between forty and fifty years of age and 1 between sixty and seventy.

c. Organs primarily affected (autopsy made in 4 cases). The stomach in 3 cases, and the rectum in 1 case. The other remaining case was perhaps the stomach.

d. Localization and structure of the skin-metastases.

Case I. The neck, the thorax, the back, and the abdomen.

Case II. The thorax and the abdomen.

Case III. The abdomen.

Case IV. The thorax and the sacral region.

Case V. The abdomen, the back, the shoulder region, the leg, the sacral region, and both inguinal regions.

As to structure and position in the skin, in 4 cases the metastases were tuberous and localized mostly in the subcutaneous

tissue while in 1 case there were diffuse flat eminences in the corium and the subcutaneous connective tissue. Four cases were adenocarcinoma, and 1 scirrhus. Of the 4 cases of adenocarcinoma, 1 was sharply defined with no increase of the connective tissue, while the other 3 had some increase of the connective tissue and were somewhat indistinctly defined; the third case showed scirrhus here and there and in this case cancer cell masses were mixed with some giant cells with giant nuclei.

e. *Type of metastasis.*

Case I. We can not exclude hematogenous metastasis as there were cancer cells in the blood-vessels of the lungs, kidneys, and the submucous stratum of the bladder. But we may assume that the skin metastases were probably lymphogenous, because lymph-capillaries and spaces in the skin were dilated here and there, and some of these capillaries and spaces contained the cancer cells, and around some sweat glands cancer cell infiltration was especially remarkable. Again, surrounding all the skin glands lay a net of lymph-vessels, narrowed at the points where they intersected (Ribbert); therefore it seems to be easy to form metastases at this place; and the regional lymph-nodes showed carcinomatous metastases and were greatly enlarged.

Case II. Owing to the following four factors, the skin metastases were hematogenous:

The nodules all appeared simultaneously.

Little or no involvement of the regional lymph-nodes was observed.

No dilatation of the lymph-vessels and spaces in the skin was seen.

The existence of cancer cells in the blood-vessels and capillaries in the metastatic growths, and also the presence of cancer cells in the blood-vessels of the lungs.

Case III. In this case the metastases were formed perhaps in the lymphatic way, owing to the following four factors: The localization of the skin metastases was only in the abdomen, and not scattered in distant places. The non-existence of cancer cells in the blood-vessels in the metastatic growths.

No existence of the metastases in the lungs and liver.

The distinct cancerous change of the regional lymph-nodes.

Case IV. The skin tumors in this case were probably hematogenous, owing to the next two factors:

The existence of the metastases in the liver and bones.

The skin metastases existed in two distant places, namely, in the chest wall and sacral region.

f. In 3 cases the patients died within about four to six weeks from the time of the first appearance of the skin-metastases while in 2 other cases the time is not exactly known.

g. Other notes.

Case I. The metastatic places were especially the connective tissues, and there the connective tissues were increased greatly.

In the growths existed abundant small round-cell infiltration, and abundant eosinophile cells were mixed with it.

There were metastases in the sympathetic ganglia in the neighborhood of the left suprarenal, so some ganglion cells showed tigrolysis and pycnosis.

Case II. Although the metastatic places were particularly the connective tissues as in the first case, this case showed no increase of the connective tissue.

The giant cells existed in the metastatic growth in the pancreas.

STATISTICAL OBSERVATIONS

The cases upon which the following conclusions are based will be found in tabular form at the end of the article.

(1) Sex. In regard to the sex I have obtained the following result:

	NUMBER OF CASES		CASES IN FOREIGN COUNTRIES		CASES IN JAPAN	
		per cent		*per cent*		*per cent*
Male	43	46.7	34	42.0	9	81.8
Female	49	53.3	47	58.0	2	18.2

According to the statistics of cancer in general, the number of the female surpasses that of the male in foreign countries, while in Japan there is a great preponderance on the side of the

male; therefore it is not to be wondered at that in the statistics of the skin metastases we find the same preponderance in the cases of female in foreign countries and of male in Japan. It should be stated that in Japan, in the primary cancer of the internal organs, there are twice as many male as female.

AUTHOR	MALE CASES		FEMALE CASES	
		per cent		*per cent*
Aschoff	1506	43.5	1956	56.5
Ishibashi and Takatsu	522	70.3	221	29.7

(2) Age. The age is mentioned in only 79 cases.

AGE	NUMBER OF CASES	PER CENT
Under 10	1	1.3
11–20	2	2.5
21–30	6	7.6
31–40	14	17.7
41–50	25	31.6
51–60	15	19.0
61–70	11	14.0
Over 70	5	6.3
Total	79	100.0

The greatest number of cases is between forty and fifty years of age, i.e., about one-third of the total. According to Paul Horn, the great majority of the acute carcinosis also is to be seen in the age between thirty-one and fifty.

(3) Organ primarily affected. In the following 97 cases of skin metastasis the primarily affected organs are accurately diagnosticated and mentioned.

The following table shows that the primary tumors are located in more than one half of the cases in the digestive organs. Of these organs, the stomach is most frequently affected; next come the uterus and the intestines, then the lungs, ovaries, etc. Riechelmann and others have demonstrated that in cases of cancer of the stomach and the esophagus, the skin metastases are comparatively few, and those of the liver, the lungs, and the ovaries rather numerous, while this was just contrary in my cases.

PRIMARY ORGAN	CASES OF SKIN METASTASIS		CANCER OF INTERNAL ORGANS (RIECHELMANN)	
	Number of cases	Per cent	Number of cases	Per cent
Stomach	33	34.0	288	48.8
Intestine	12	12.4	59	10.0
Esophagus	4	4.1	77	13.1
Pharynx	2	2.1	4	0.7
Liver	4	4.1	3	0.5
Pancreas	2	2.1	19	3.2
Uterus	15	15.5	86	14.6
Ovaries	5	5.2	14	2.4
Kidneys	2	2.1	2	0.3
Suprarenal	2	2.1		
Bladder	1	1.0	6	1.0
Thyroid gland	2	2.1	5	0.8
Lungs	7	7.2	27	4.6
Bronchus	3	3.1		
Trachea	1	1.0		
Mediastinum	2	2.1		

The following table (from the statistics of Redlich and Feilchenfeld) shows the percentage of metastases in general:

PRIMARY ORGAN	REDLICH	FEILCHENFELD
	per cent	*per cent*
Mamma	100.0	96.2
Pancreas	100.0	77.0
Lungs	96.6	71.4
Bile-ducts	93.7	92.3
Kidneys	87.5	
Ovaries, vagina and vulva	86.7	
Stomach	84.0	85.8
Uterus Uterus and vagina	79.5	59.5
Esophagus	75.0	76.8
Pharynx	72.7	
Large intestine	70.0	53.2
Rectum	69.6	66.7

From this table it is apparent that in the case of primary cancer of the internal organs, metastases are most often formed from cancers of the pancreas, bile-ducts, lungs, etc., and less fre-

quently in cancer of the esophagus, pharynx, large intestine, rectum, etc.

Next, the duration of life of the patients must be noted. According to Paul Horn's investigation, cancers of the liver and pancreas progress most rapidly; next those of the lungs and kidneys, as shown in the following tables:

PRIMARY ORGAN	PERCENTAGE OF ACUTE CARCINOSIS. (THE PATIENTS DIE BEFORE THREE MONTHS HAVE ELAPSED)
Liver	40.1
Pancreas	37.5
Lungs	23.7
Kidneys	15.4
Suprarenals	14.3
Thyroid gland	10.2
Small intestine	8.0
Stomach	3.4

The preceding facts confirm the following statement made by Sudo: Although cancers of the liver and pancreas are more liable to form metastases, there is not sufficient time for the formation of skin metastases because the patients die before the cancer cells can develop in some part of the body distant from the primary organs.

(4) Types of cancers.

NO.	TYPES	NUMBER OF CASES	PER CENT	ACUTE CARCINOSIS (PAUL HORN)
				per cent
1	Adenocarcinoma (medullary cancer)	27	58.7	84.0
2	Scirrhus	11	23.9	11.7
3	Gelatinous cancer	3	6.5	4.3
4	Squamous cell cancer	3	6.5	
5	Basal cell cancer	2	4.4	
	Total	46	100.0	100.0

This table shows that adenocarcinoma and medullary cancer most often produce acute carcinosis; next comes scirrhus.

(5) Localization of metastatic tumors in the skin.

The following table mentions only those cases in which the localization of the skin metastases is given in the literature together with my 5 cases.

NO.	LOCALIZATION	NUMBER OF CASES	PER CENT
1	Cutis and subcutis stratum	36	55.4
2	Subcutis	29	44.6

So I can say that skin metastases develop mostly in the cutis and subcutis simultaneously or in the subcutis only.

(6) Form, number, and size of the metastatic growths in the skin.

The forms of the skin metastases may be classified into circumscribed and diffuse, as follows:

NO.	FORM	NUMBER OF CASES	PER CENT
1	Circumscribed	66	90.4
2	Diffuse	5	6.9
3	Two forms mixed	2	2.7

It is evident from this table that cancer forms metastases in the skin mostly in nodular form, while diffuse infiltration is very rare. I found 3 instances of lymphatic infarction (carcinomatous) in 5 cases of diffuse form, but only 4 cases of it out of 66 cases of nodular form and 1 case of it out of 2 cases of the two forms mixed.

The size of the metastatic tumors in the skin varies according to the growth of the cancer and the duration of the patient's life. In the case of multiple skin metastases, large nodules of different sizes, varying from the size of a pea to that of a walnut, are most numerous, while those of miliary size and those so small as to be hardly perceptible are very scarce; I have found only 4 cases (Röseler, Frank, Regnault, and my case II). Growths as large as a hen's egg are also rare (Sudo, Levi, Reitmann, Clairmont, and my case V).

The diffuse tumors vary in extent and in size. Schlagenhaufer's case is probably the most advanced, that is, the skin metastases spread over the front and back neck regions, both supraclavicular fossae, the whole thorax and right abdominal side, backwards to the vertebral column, and the right arm. Next comes Mannoury's case. It was comparatively advanced, having spread over the whole right side of the neck and below the clavicle to the subclavicular triangle. In Geipel's case it was over the whole neck, being particularly stiffly infiltrated on the right side. In Kayser's case it was formed of many different sized metastatic growths, the largest being the size of a palm, located in the left thigh. In Rusch's case it was infiltrated in the supraclavicular fossa. The widest infiltration I have seen was in my case I; it was half as large as a palm and located at the right side of the neck.

(7) Localization of the skin metastases. I have found 81 cases in which the localization of the metastatic growths is mentioned.

LOCALIZATION	NUMBER OF CASES
All over the body	10
Thorax	37
Abdomen	39
Face	4
Head (occiput)	8
Neck	11
Nape of neck	3
Back, lumbar, and sacral regions	15
Arm (hand)	15
Leg	15
Shoulder region	5
Inguinal region	3
Around the labium	1

Thus the abdomen and thorax seem to be the favorite seats of the skin metastases. In other words, the skin metastases are more frequently found on the trunk than in the limbs; more on the abdomen and chest than in the dorsal and lumbar regions. Also when the limbs are affected, it is more on the extensor than on the flexor side.

The localization of the skin metastases is variously accounted for.

1. According to Ribbert, around every gland and hair-follicle in the skin there is a network of intersecting lymph-vessels; therefore, it seems easy to form metastases at these places. This hypothesis may apply to my case I where the cancer cell infiltration around the sweat glands was so extensive. However, I have not found such changes in other cases.

2. In some cases the skin metastases appeared after a herpetic eruption or other skin affection (Schmidt and Mignon), but I found none in any of my cases.

3. Reitmann says that as among stomach cancers forming skin metastases the scirrhous type is quite frequent, the metastases seem to be formed according to the "organ relationship theory" in the similar tissues, viz., in the skin, which has many connective tissues. According to my statistics of stomach cancers with skin metastases, however, there were 8 scirrhus out of 22 (36.4 per cent) and regarding the cancers in all internal organs, there were only 11 cases of scirrhus out of 46 cases (23.9 per cent). Although in some cases many metastatic growths were formed in the skin and other connective tissues, none were formed in organs with few connective tissues (Reitmann, Röseler, Emanuel, Sudo's case III, Kaufmann-Wolf, and my case I). Among these cases, those of Reitmann, Kaufmann-Wolf, and Suzuki were scirrhus. These cases are, however, very rare.

Adenocarcinoma and medullary cancer form skin metastases more frequently than scirrhus. This theory seems to apply therefore only to these few cases.

As to the reason why metastasis takes place on the abdomen and thorax, the following explanations are given.

1. Places full of wrinkles, says Lereboullet, are the most favorite situations of the skin metastases. But the axillary fossa, scrotum, inguinal region, popliteal space, etc., have by far more wrinkles than the abdomen and thorax; yet these localities are not favorite ones for skin metastases.

2. According to Sudo, it is due entirely to the disposition of the places that the thorax and abdomen are the best substratum for the skin metastases.

The favorite situation and the paths of the metastases are not wholly unrelated, so I shall try to make some explanation of this relationship.

There are three modes of forming the skin metastases.

1. The continuous infiltrating growth.
2. The hematogenous metastasis.
3. The lymphogenous metastasis.

I shall now describe in what way the lymphatic metastases reach the skin. In the case of primary cancer of the organs in the thorax, the cancer cells affect the bronchial and tracheal lymph-nodes first, next the cervical, supraclavicular, and axillary nodes. Through these the metastases reach the skin.

The lymph-channels of the lungs, bronchi, lower part of the trachea, and some from the esophagus and the heart flow into the bronchial nodes. The lymphatic stream from the bronchial nodes flows into the bronchomediastinal trunk and vein-angle. The connecting point of the paratracheal and tracheobronchial nodes with supraclavicular is the important flowing way. The lateral group of the supraclavicular nodes connects with the axillary nodes. It is possible that the metastases are formed from these nodes retrograding in the skin of the thorax, shoulder, and arm.

In some cases the metastases are formed from the thoracic organs retrograding into the abdominal organs or their lymphatic nodes.

The primary cancer of the abdominal organs forms metastases in the retroperitoneal lymph-nodes. From these the cancer cells pass through the lymphatic vessels to the cervical, supraclavicular, intraclavicular, and axillary nodes. Thus the metastases are formed in the skin.

In other cases, the metastases are formed in the iliac first; next in the inguinal lymph-nodes, so the cancer cells reach the skin through the vasa lymphatica superficialia abdominis.

In some cases, however, the metastases pass from the iliac to the lower epigastric lymph-nodes and on to the navel ring.

There are probably still other ways: namely, from the retroperitoneal nodes through the vasa lymphatica profunda abdom-

inis, then through the vasa lymphatica superficialia abdominis to the skin. From the periportal lymphatic nodes to the navel via ligamentum teres hepatis. So it is not infrequently that metastases are formed at the navel.

In the before stated lymphatic paths, the metastases are formed most frequently over the abdomen and thorax. In cases where the limbs are affected, it is quite frequently the flexor side. It is not to be wondered at that this should be so in the case of lymphatic metastases, if we stop to think that the lymphatic system is more developed anatomically on the flexor side of the limbs and on the thorax and abdomen, than on the extensor side or in the dorsal and lumbar regions.

It is very seldom, however, that we find both navel and skin metastases in the same case, and of the 166 cases before mentioned, only 4 were described as navel metastases (Cahn, Spiegelberg, Freund, and Stropeni).

Metastases rarely exist in the regional skin when the inguinal, cervical, and axillary nodes are distinctly swollen. Although these lymph-nodes are greatly enlarged and metastases exist in the regional skin, we can not easily pronounce it to be lymphogenous metastasis, because it may be posssible that, through the skin metastases, the regional nodes are secondarily swollen. It is difficult to decide which were swollen first.

Next I shall describe the blood-vessels. According to the reports of Spalteholz, Lewinski, and others, in the palm of the hand, the sole of the foot, the gluteal and patellar regions, etc., where there is much external pressure, there are many blood-vessels. There are few, however, in the skin of the abdomen and here there are few anastomoses. In the back there are more blood-vessels and more anastomoses. In the limbs, the blood-vessels are generally more numerous on the flexor than on the extensor side. Therefore the skin metastases are formed apparently more on the side where there are few blood-vessels.

Accordingly, the question why the metastases of the cancer cells on the skin of the thorax and abdomen are of frequent occurrence, is difficult to answer. A careful consideration of the anatomical distribution and condition of the blood- and

lymph-vessels in these regions may throw light to some though not to sufficient extent. I support Sudo in the statement that it is due to the disposition of the place that the abdomen and thorax are the favorite situations of the skin metastases.

(8) Clinical observations.

Clinical diagnosis of skin metastases is sometimes very difficult, especially when the symptoms of the primary cancer do not manifest themselves (Lippmann, Vierth, Beitzke, Stropeni, Clairmont, Sudo, etc.). In such cases it is necessary to differentiate them from sarcomatosis cutis, multiple fibromata, metastatic endothelioma (Riehl's case), mycosis fungoides, leukemia, etc.

There are some cases which have been diagnosed as other tumors; namely, Göbel's case as fibrolipoma, Sudo's case as multiple fibroma, Reitmann's, Joseph's, and Sudo's cases as sarcomatosis cutis. It is decided in most cases by the histological observation, but there are some cases which have histological representations which increase the difficulty of decision (Reitmann). When the skin tumor is microscopically the adenocarcinoma, there is no doubt that it is mostly cancer of the digestive organs, though there is no pathological symptom ((Ziegler, Stropeni, and Sudo). Especially when it has any liver cells, we can at once diagnose it as the cancer of the liver (Clairmont). When the skin metastases appear, the prognosis is naturally absolutely bad, as there is no good treatment for it. I have made investigations concerning the duration of life from the appearance of the skin tumor to the death of the patients as follows:

TIME BETWEEN THE FIRST APPEARANCE OF SKIN METASTASES AND DEATH OF PATIENT	NUMBER OF CASES
Within a month	12
One to three months	10
Three to six months	12
One-half to one year	2
More than one year	2

Thus I can say that most of the patients die within three months from the first appearance of the skin metastases.

SUMMARY

1. As to the sex of the patients observed in Japan, out of 11 cases, 9 were male, including the writer's cases.

2. Skin metastasis usually occurs between the ages of forty to fifty.

3. In the majority of cases it has its origin in the digestive organs, which are undoubtedly the most favorite seats of the tumor.

4. In most instances the tumor is adenocarcinoma and medullary cancer.

5. The skin metastases develop mostly in both the cutis and subcutis simultaneously or in the subcutis alone.

6. The circumscribed nodules, pea to walnut in size, are the most frequent, while the infiltrating form is exceedingly rare.

7. The cutaneous surfaces of the thorax and abdomen are the favorite seats of the metastases.

8. Occasionally it is difficult to diagnose the lesion without histological examination.

9. The prognosis is always grave, most cases terminating fatally within three months from the time of the first appearance of the skin metastases.

TABLES

NO.	AUTHOR	SEX	AGE	SEAT OF PRIMARY TUMOR	HISTOLOGICAL TYPE	LOCALIZATION OF SKIN METASTASES	LOCALIZATION OF TUMOR IN SKIN	FORM OF METASTATIC SKIN TUMOR	TIME BETWEEN FIRST APPEARANCE OF SKIN METASTASES AND DEATH
1	Sudo	F	42	Stomach	Medullary cancer	Face, neck, thorax, abdomen, shoulder, and left arm	Cutis and subcutis	Nodular	6 weeks
2	Sudo	M	56	Stomach?	Adenocarcinoma	Thorax, abdomen, shoulder, back, and both thighs	Subcutis	Nodular	5 months
3	Sudo	M	30	Stomach	Adenocarcinoma	Whole body, especially thorax and abdomen	Cutis and subcutis	Nodular	5 months
4	Sudo	M	65	?	Adenocarcinoma	Back and right thigh		Nodular	
5	Arning	M	40	Stomach?	Adenocarcinoma	Whole body	Subcutis	Nodular	
6	Lippmann	M	67	Stomach		Thorax, abdomen, arm above elbow, and both thighs	Cutis and subcutis	Nodular	3 weeks
7	Regnault	F	67	Stomach			Subcutis	Nodular	5 months
8	Joseph	M	32	Stomach	Scirrhus	Whole body	Subcutis and cutis	Nodular	5 months
9	Babes and Stoicesco	M	45	Stomach	Adenocarcinoma	Whole body	Subcutis	Nodular	3 months
10	Röseler	F	47	Stomach		Whole body, especially abdomen	Cutis and subcutis	Nodular	7 months
11	Daus	F	77	Stomach	Scirrhus	Whole body, especially thorax, abdomen, neck, and thigh	Subcutis	Nodular	

12	Daus	F	48	Stomach	Scirrhus	Front part of thorax	Subcutis	Nodular	
13	Reitmann	F	33	Stomach	Scirrhus	Especially abdomen and thorax	Cutis and subcutis	Nodular	5 months and 2 weeks
14	Beitzke			Stomach	Medullary cancer		Subcutis	Nodular	
15	Oguro	M	44	Stomach	Scirrhus	Head, face, neck, thorax, abdomen, and back	Cutis and subcutis	Nodular	2 months
16	Kreibich	F	65	Stomach	Scirrhus	Thorax, abdomen, and neck	Cutis and subcutis	Nodular	1 year and 6 months
17	Ziegler			Stomach	Adenocarcinoma	Left arm, especially	Cutis and subcutis	Nodular (Lymphatic infarction)	8 months
18	Vierth	M	42	Stomach	Adenocarcinoma		Subcutis	Nodular	About 4 months
19	Merklen	F	68	Stomach		Thorax and abdomen	Cutis and subcutis	Nodular	
20	Brieger	F	44	Stomach		Thorax	Subcutis	Nodular	2 weeks
21	Cited by Krasting			Stomach					
22	Cited by Krasting			Stomach					
23	Mielecki			Stomach					
24	Lex			Stomach					
25	Lex			Stomach					
26	Nishida	M	67	Stomach?		Thorax and inguinal region			
27	Boinet and Olmar	M	53	Stomach		Thorax	Subcutis	Nodular	1 month

NO.	AUTHOR	SEX	AGE	SEAT OF PRIMARY TUMOR	HISTOLOGICAL TYPE	LOCALIZATION OF SKIN METASTASES	LOCALIZATION OF TUMOR IN SKIN	FORM OF METASTATIC SKIN TUMOR	TIME BETWEEN FIRST APPEARANCE OF SKIN METASTASES AND DEATH
28	Mannoury	F	41	Stomach	Scirrhus	Neck	Cutis and subcutis	Diffuse infiltration	3 weeks
29	Tilling	M	42	Stomach	Adenocarcinoma	Abdomen and left hypochondrium	Cutis and subcutis	Nodular	1 month
30	Vidal	M	50	Stomach		Epigastrium		Nodular	
31	Lionville	M	58	Stomach			Cutis and subcutis	Nodular	1 week
32	Dusaussay	M	43	Stomach		Region of the left vii and xi ribs	Subcutis	Nodular	2 weeks
33	Milner	M	60	Stomach?		Abdomen			
34	Schlagenhaufer	F	20	Stomach?	Mucous cancer	Neck, thorax, abdomen, back and right arm	Cutis and subcutis	Diffuse infiltration (Lymphatic infarction)	
35	Moutier and Marre	F	31	Stomach		Subclavicular region, mamma, and left arm	Cutis and subcutis	Nodular (Lymphatic infarction)	2 weeks
36	Geipel	M	38	Stomach	Adenocarcinoma	Neck, shoulder, and right arm (upper part)	Cutis and subcutis	Diffuse infiltration (Lymphatic infarction)	3 weeks
37	Rusch	M	38	Stomach?		Supraclavicular fossa	Cutis and subcutis	Diffuse infiltration (Lymphatic infarction)	

38	Cahn	M	45	Stomach?		Abdomen, including umbilicus			
39	Suzuki	M	46	Stomach	Scirrhus	Neck, thorax, back, and abdomen	Cutis and subcutis	Diffuse infiltration	6 weeks
40	Suzuki	M	43	Stomach	Adenocarcinoma	Thorax and abdomen	Cutis and subcutis	Nodular	6 weeks
41	Suzuki	F	44	Stomach	Adenocarcinoma	Abdomen	Subcutis	Nodular	
42	Suzuki	M	43	Stomach?	Adenocarcinoma	Leg, sacral region, shoulder, back, abdomen, both inguinal regions	Subcutis	Nodular	
43	Krasting	M	72	Pharynx					
44	Krasting	M	62	Pharynx		Abdomen			
45	Levi	M	48	Esophagus		Left leg	Subcutis	Nodular	2 months
46	Pigger			Esophagus		Thorax		Nodular	
47	Pigger			Esophaus		Thorax		Nodular	
48	Lex			Esophagus					
49	Müller, Max			Small intestine		Trunk			
50	Göbell	M	60	Stomach or small intestine	Gelatinous cancer	Abdomen	Subcutis	Nodular	
51	Laache	M	46	Large intestine		Abdomen, inguinal region, and right thigh	Subcutis	Nodular	
52	Kayser	F	57	Large intestine	Adenocarcinoma	Abdomen and left thigh	Cutis and subcutis	Diffuse infiltration and nodular (Lymphatic infarction)	2 months and 2 weeks

NO.	AUTHOR	SEX	AGE	SEAT OF PRIMARY TUMOR	HISTOLOGICAL TYPE	LOCALIZATION OF SKIN METASTASES	LOCALIZATION OF TUMOR IN SKIN	FORM OF METASTATIC SKIN TUMOR	TIME BETWEEN FIRST APPEARANCE OF SKIN METASTASES AND DEATH
53	Charcot			Large intestine					
54	Mielecki			Intestine					
55	Mielecki			Intestine					
56	Lustgarten	M	50	Rectum		Whole body	Subcutis	Nodular	
57	Quenu-Hartmann			Rectum					
58	Lereboullet	M	71	Rectum	Adenocarcinoma	Left shoulder	Cutis and subcutis	Nodular	
59	Simon	F		Rectum	Squamous cell carcinoma	Thorax and abdomen	Subcutis	Nodular	1 month
60	Nobl	M	40	Rectum		Head, trunk, and supraclavicular fossa		Nodular	
61	Landois	M	56	Rectum	Adenocarcinoma	Occiput		Nodular	
62	Redlich	F		Large intestine or ovary		Trunk			
63	Suzuki	M	61	Rectum	Adenocarcinoma	Thorax and sacral region	Subcutis	Nodular	About 4 weeks
64	Babes and Stoicesco	F	42	Uterus	Adenocarcinoma	Whole body, especially lumbar region, neck, and arm (upper part)	Subcutis	Nodular	
65	Lorrain	F		Uterus					
66	Lex	F		Uterus					
67	Lex	F		Uterus					

68	Virchow	F		Uterus		Trunk and left thigh	Cutis and subcutis	Nodular and diffuse infiltration	
69	Petersen	F	50	Uterus	Matrix (basal cell) carcinoma	Thigh and around the labium	Cutis and subcutis	Nodular	
70	Dybowski	F		Uterus					
71	Clairmont	F	50	Uterus	Basal cell carcinoma	Leg	Cutis and subcutis	Nodular	2 years
72	Clairmont	F	50	Uterus		Left thigh		Nodular	
73	Blau	F		Uterus	Cancroid	Below right mamma			
74	Blau	F		Uterus		Thorax and abdomen			
75	Elschnig	F	73	Uterus				Nodular	
76	Joseph	F		Uterus			Cutis and subcutis	Nodular (Lymphatic infarction)	
77	Kroemer	F	55	Uterus			Cutis and subcutis		
78	Buday	F		Uterus					
79	Emanuel	F	60	Ovary	Adenocarcinoma	Abdomen (cicatrix of operation and other parts)	Subcutis	Nodular	
80	Briegelberg	F	19	Ovary		Abdomen			
81	Spiegelberg	F		Ovary		Abdomen and umbilicus		Nodular	
82	Frank	F	24	Ovary	Adenocarcinoma	Abdomen (cicatrix of operation and inside border of patella)	Cutis and subcutis	Nodular	
83	Freund	F		Ovary or uterus		Abdomen, including umbilicus		Nodular	
84	Buday	F		Ovary					

NO.	AUTHOR	SEX	AGE	SEAT OF PRIMARY TUMOR	HISTOLOGICAL TYPE	LOCALIZATION OF SKIN METASTASES	LOCALIZATION OF TUMOR IN SKIN	FORM OF METASTATIC SKIN TUMOR	TIME BETWEEN FIRST APPEARANCE OF SKIN METASTASES AND DEATH
85	Harrison	F	50	Ovary?		Trunk, neck, head, etc.			
86	Lex			Lung					
87	Japha	M	58	Lung		Abdomen	Cutis and subcutis	Nodular	4 months
88	Handford	M	40	Lung		Head, episternal fossa, left arm, left thigh	Subcutis	Nodular	3 months
89	Heimann			Lung					
90	Heimann			Lung					
91	Krasting			Lung					
92	Krasting			Lung					
93	Stropeni	F	35	Bronchus	Adenocarcinoma	Left arm, umbilicus, and Mohrenheim's fossa	Subcutis	Nodular	
94	Redlich			Bronchus		Whole body			
95	Dömeney	M	29	Bronchus					
96	Pick			Trachea		Finger			
97	Sänger	M	35	Mediastinum		Head	Subcutis		3 weeks
98	Schmidt	F	62	Mediastinum		Neck, thorax (mamma), and left arm	Cutis and subcutis	Nodular	
99	Moreau		3*	Kidney			Subcutis		
100	Winkler	M	45	Kidney	Adenocarcinoma	Neck, back, and palm of hand			
101	Laache	M	63	Kidney and suprarenals		Thorax, abdomen, and right arm	Subcutis	Nodular	

* Months.

102	Chaillous	M	27	Suprarenal		Head, face, thorax, abdomen, and limbs	Cutis and subcutis	Nodular	4 months
103	Robert	M	27	Suprarenal					
104	Kaufmann Wolf	F	54	Liver	Scirrhus	Thorax and neck	Cutis and subcutis	Nodular (Lymphatic infarction)	About 4 months
105	Clairmont	M	52	Liver	Adenocarcinoma	Occiput	Subcutis	Nodular	
106	Friedreich	F	37	Liver	Scirrhus	Thorax and abdomen	Cutis and subcutis	Nodular	3 months
107	Stahr	F	35	Liver	Medullary cancer	Right middle finger			
108	Dahms	F	69	Pancreas		Whole body	Cutis and subcutis	Nodular	5 months
109	Preti	M	72	Pancreas	Squamous cell carcinoma		Subcutis	Nodular	
110	Fillié	F	60	Thyroid gland	Adenocarcinoma		Cutis and subcutis	Nodular	6 months
111	Winiwarter	F	35	Thyroid gland	Medullary cancer				
112	Azúa	M	60	Bladder	Scirrhus	Thorax and abdomen	Cutis and subcutis	Nodular	
113	Hanot	F	22	Between uterus and bladder	Colloid cancer	Epigastric region and thorax	Subcutis	Nodular	
114	Heuss	F	31	?		Right forearm, nose and ear		Nodular	6 months
115	Müller, O.	F	52	?		Thorax and neck	Cutis and subcutis	Nodular	

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